



US006632795B1

(12) **United States Patent**  
**Barlozzari et al.**

(10) **Patent No.:** **US 6,632,795 B1**  
(45) **Date of Patent:** **\*Oct. 14, 2003**

(54) **DOLASTATIN-15 DERIVATIVES IN COMBINATION WITH TAXANES**

(75) Inventors: **Teresa Barlozzari**, Wellesley, MA (US); **Andreas Haupt**, Northborough, MA (US)

(73) Assignee: **BASF Aktiengesellschaft** (DE)

(\* ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/520,254**

(22) Filed: **Mar. 7, 2000**

**Related U.S. Application Data**

(63) Continuation of application No. 08/819,101, filed on Mar. 13, 1997, now Pat. No. 6,103,698.

(51) **Int. Cl.**<sup>7</sup> ..... **A61K 38/00**; A61K 31/335

(52) **U.S. Cl.** ..... **514/18**; 514/17; 514/16; 514/449

(58) **Field of Search** ..... 514/18, 17, 16, 514/449

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

4,816,444 A	3/1989	Pettit et al.	514/17
4,879,278 A	11/1989	Pettit et al.	514/17
5,227,400 A	7/1993	Holton et al.	514/444
5,248,796 A	9/1993	Chen et al.	549/510
5,250,683 A	10/1993	Holton et al.	544/60
5,254,580 A	10/1993	Chen et al.	514/449
5,272,171 A	12/1993	Ueda et al.	514/449
5,278,324 A	1/1994	Kingston et al.	549/510
5,447,936 A	9/1995	Hausheer et al.	514/283
5,484,612 A	1/1996	Brown	424/649
5,494,930 A	2/1996	Shimizu et al.	514/450
5,502,032 A	3/1996	Haupt et al.	514/17
5,504,191 A	4/1996	Pettit et al.	530/330
5,525,613 A	6/1996	Wynn et al.	514/304
5,530,097 A	6/1996	Pettit et al.	530/330
5,543,423 A	8/1996	Zelle et al.	514/332
5,565,478 A	10/1996	Kohn et al.	514/359

**FOREIGN PATENT DOCUMENTS**

EP	0 398 558	11/1990
EP	0 598 129 A1	5/1994
FR	2 697 752	5/1994
WO	WO 92/09589	6/1992
WO	WO 93/18210	9/1993
WO	WO 94/10995	5/1994
WO	WO 95/08994	4/1995
WO	WO 95/19769	7/1995
WO	WO 96/18401 A1	6/1996
WO	WO 96/40751	12/1996
WO	WO 96/40752	12/1996

**OTHER PUBLICATIONS**

Rose, W.C., "Taxol-Based Combination Chemotherapy and Other In Vivo Preclinical Antitumor Studies", *J. of the National Cancer Institute Monographs* (15):47-53 (1993).

Holton, R.A., et al., "First Total Synthesis of Taxol. 1. Functionalization of the B Ring," *J. Am. Chem. Soc.*, 116:1597-1601 (1994).

Nicolaou, K.C., et al., "Total Synthesis of Taxol," *Nature*, 367:630-634 (1994).

Kumar, N., "Taxol-induced Polymerization of Purified Tubulin," *J. Biol. Chem.* 256:10435-10441 (1981).

Rowinsky, E.K., et al., "Taxol: A Novel Investigational Antimicrotubule Agent," *J. Nat'l Cancer Inst.*, 82:1247-1259 (1990).

Schiff, P.B., et al., "Promotion of Microtubule Assembly in vitro by taxol," *Nature*, 277:665-667 (1979).

McGuire, W.P., et al., "Taxol: A Unique Antineoplastic Agent with Significant Activity in Advanced Ovarian Epithelial Neoplasms," *Ann. Int. Med.*, 111:273-279 (1989).

Holmes, F., et al., "Phase II Trial of Taxol, an Active Drug in the Treatment of Metastatic Breast Cancer," *J. Nat'l Cancer Inst.*, 83:1797-1805 (1991).

Kohn, E., et al., "A Pilot Study of Taxol, Cisplatin, Cyclophosphamide, and G-CSF in Newly Diagnosed Stage III/IV Ovarian Cancer Patients," *Am. Society for Clinical Oncology*, 12: Abstract 814 (1993).

Bai, R., et al., "Structure-Activity Studies with Chiral Isomers and with Segments of the Antimitotic Marine Peptide Dolastatin 10," *Biochem. Pharmacology*, 40:1859-1864 (1990).

Kohn, E.C., et al., "Dose-Intense Taxol: High Response Rate in Patients with Platinum-Resistant Recurrent Ovarian Cancer," *J. Nat'l Cancer Inst.*, 86:18-24 (1994). Abstract \*814.

Leopold, W., et al., "Therapeutic Synergy of Trimetrexate (C1-898) in Combination with Doxorubicin, Vincristine, Cytosin, 6-Thioguanine, Cisplatin, or 5-Fluorouracil Against Intraperitoneally Implanted P388 Leukemia," *NCI Monographs*, (5):99-104 (1987).

Schabel, Jr., F.M., et al., "Quantitative Evaluation of Anticancer Agent Activity in Experimental Animals," *Pharmac Ther. A.*, 1:411-435 (1977).

Chou, T.-C., et al., "Computerized Quantitation of Synergism and Antagonism of Taxol, Topotecan, and Cisplatin Against Human Teratocarcinoma Cell Growth" a Rational Approach to Clinical Protocol Design, *J. of the National Cancer Institute*, 86(20):1517-1524 (1994).

(List continued on next page.)

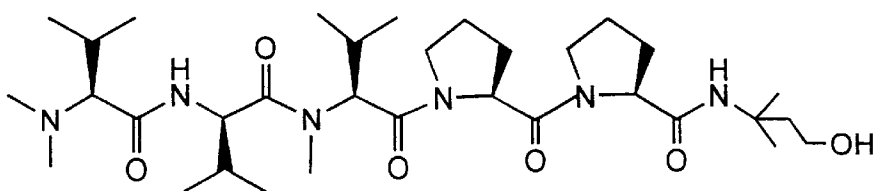
*Primary Examiner*—Jerome D. Goldberg  
(74) *Attorney, Agent, or Firm*—Lahive & Cockfield, LLP; Peter C. Lauro, Esq.; Giulio A. DeConti, Esq.

(57) **ABSTRACT**

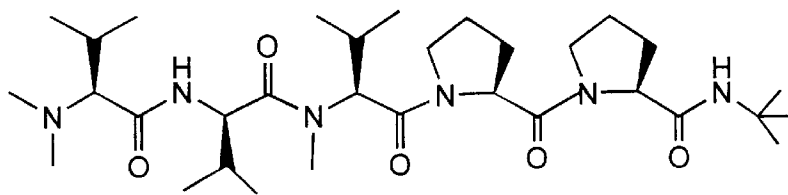
The present invention provides compositions and methods for the treatment of cancer in a subject wherein compounds of Formula I as defined herein in combination with paclitaxel, taxotere or modified taxane or taxoid analogs provide enhanced anticancer effects over the effects achieved with the individual compounds.

## OTHER PUBLICATIONS

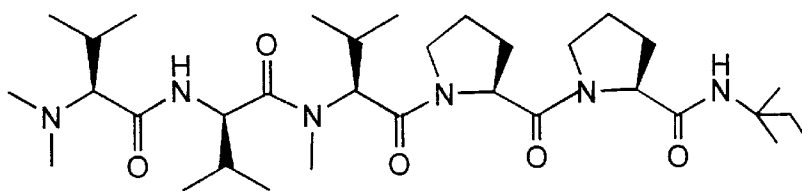
- Knick, V.C., et al., "Vinorelbine Tartrate and Paclitaxel Combinations: Enhanced Activity Against In Vivo P388 Murine Leukemia Cells," *J. of the National Cancer Institute*, 87(14):1072-1077 (1995).
- Bissery, M.C., et al., "Docetaxel in combination with vinorelbine: Preclinical-clinical correlation," *Proc. Am. Soc. Clin. Oncol. 15 32 Meet*, 48:(1996) Abstract 96-43670.
- Beckwith, M., et al., "Growth Inhibition of Human Lymphoma Cell Lines by the Marine Products, Dolastatins 10 and 15," *J. Nat'l Cancer Inst.*, 85:483-488 (1993).
- Freidinger, R., et al., "Protected Lactam-Bridged Dipeptides for Use as Conformational Constraints in Peptides," *J. Org. Chem.*: 104-109 (1982).
- Galeotti, N., et al., "Formation of Oxazolines and Thiazolines in Peptides by the Mitsunobu Reaction," *Tetrahedron Letters*, 33(20): 2807-2810 (1992).
- Wipf, P., et al., "A Short, Stereospecific Synthesis of Dihydrooxazoles from Serine and Threonine Derivatives," *Tetrahedron Letters*, p. 907-910 (1992).
- Tully, W.R., et al., "2-(Oxadiazolyl)- and 2-(Thiazolyl)imidazo[1,2-a]pyrimidines as Agonists and Inverse Agonists at Benzodiazepine Receptors," *J. Med. Chem.*, 34:2060-2067 (1991).
- Miyazaki, K., et al., "Synthesis and Antitumor Activity of Novel Dolastatin-10 Analogs," *Chem. Pharm. Bull.*, 43(10):1706-1718 (1995).
- Pettit, G.R., et al., "The Isolation and Structure of a Remarkable Marine Animal Antineoplastic Constituent: Dolastatin 10," *J. Am. Chem. Soc.*, 109:6883-6885 (1987).
- Pettit, G.R., et al., "Antineoplastic Agents 337. Synthesis of Dolastatin-10 Structural Modifications," *Anti-Cancer Drug Design*, 10:529-544 (1995).
- Pettit, G.R., et al., "Antineoplastic Agents 220. Synthesis of Natural (-)- Dolastatin 15," *J. Am. Chem. Soc.*, 113:6692-6693 (1991).
- Bai, R., et al., "Dolastatin 15, a potent antimitotic depsipeptide derived from *Dolabella auricularia*. Interaction with tubulin and effects on cellular microtubules," *1-Pharmacology, Abstract 117*: 103735g p. 41 (1992).
- Pettit, G.R., et al., "Isolation and Structure of the Cytostatic Depsipeptide Dolastatin 13 from the Sea Hare *Dolabella auricularia*," *J. Am. Chem. Soc.* 111(13): 5015-5017 (1989).
- Schmidt, U., et al., "Amino Acids and Peptides; 59. Synthesis of Biologically Active Cyclopeptides; 9. Synthesis of 16 Isomers of Dolastatin 3; I. Synthesis of the 2-(1-aminoalkyl)-thiazole-4-carboxylic Acids," *Synthesis*: 233-236 (Mar. 1987).
- Pettit, G.R., et al., "Isolation and Structure of the Cytostatic Linear Depsipeptide Dolastatin 15," *J. Org. Chem.*, 54:6005-6006 (1989).
- Conlon, D., et al., "In vivo antitumor activity of LU103793 in combination with Taxol," *J. of Cancer Research*, 38:320 (Mar. 21, 1997). (From *Proceedings of the American Association for Cancer Research Annual Meeting*, 1997, Abstract No. 2142).



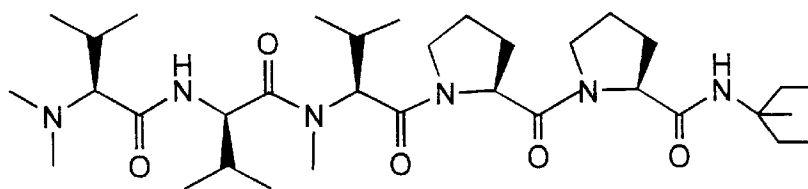
(i)



(ii)

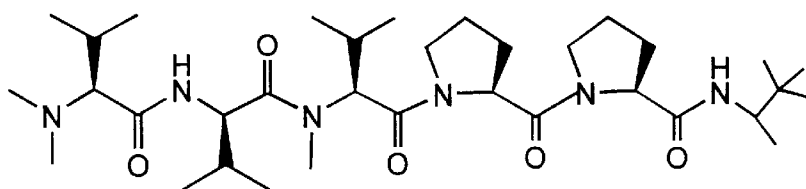


(iii)

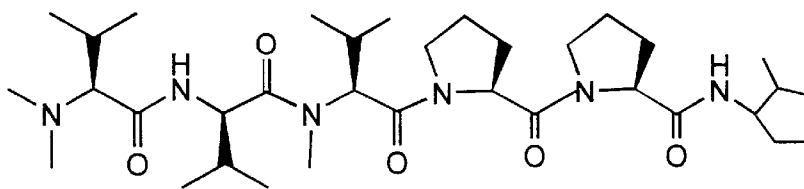


(iv)

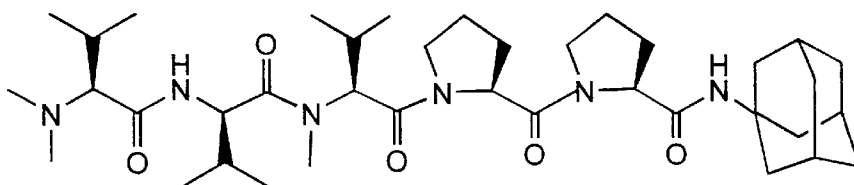
FIG. 1A



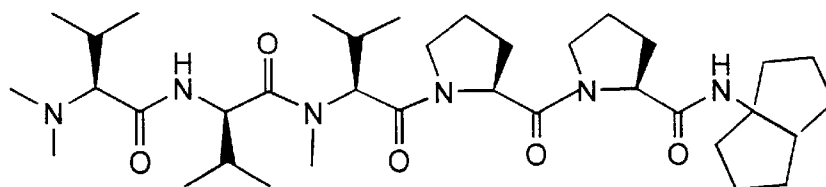
(v)



(vi)

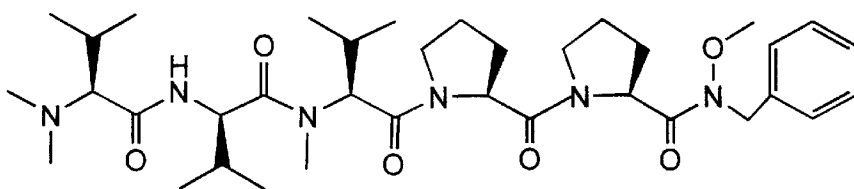


(vii)

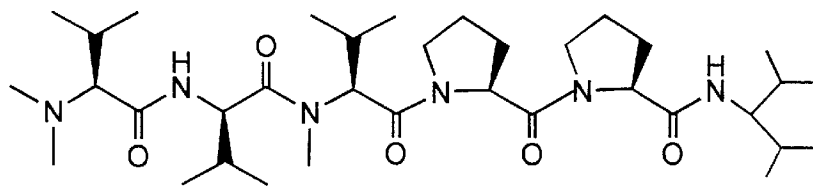


(viii)

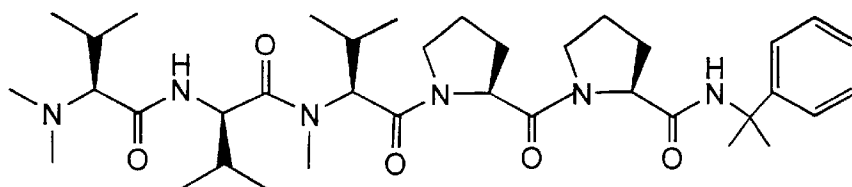
FIG. 1B



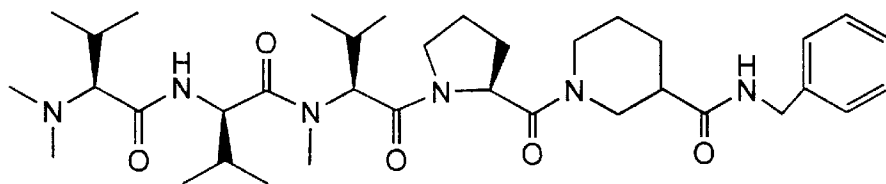
(ix)



(x)

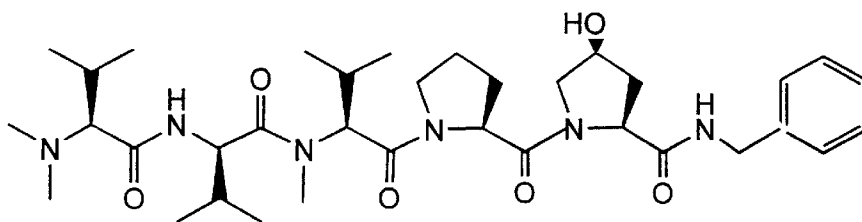


(xi)

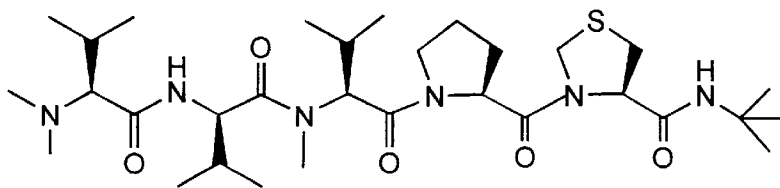


(xii)

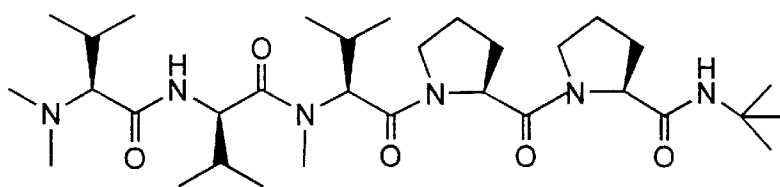
FIG. 1C



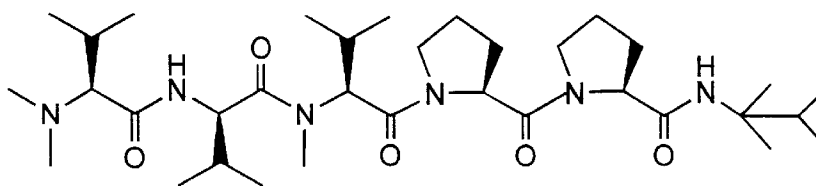
(xiii)



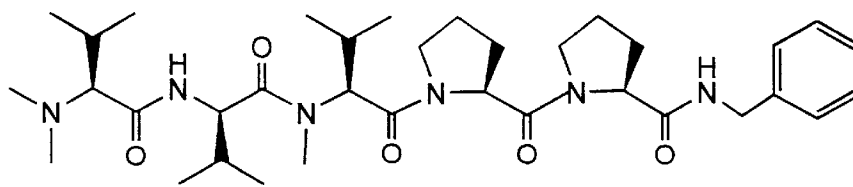
(xiv)



(xv)



(xvi)



(xvii)

FIG. 1D

# DOLASTATIN-15 DERIVATIVES IN COMBINATION WITH TAXANES

## RELATED APPLICATIONS

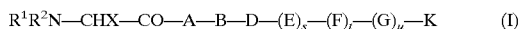
This application is a Continuation of U.S. Ser. No. 08/819, 101, filed Mar. 13, 1997 now U.S. Pat. No. 6,103,698, the entire teachings of which are incorporated herein by reference.

## BACKGROUND OF THE INVENTION

Cancer is a disease for which many potentially effective treatments are available. However, due to the prevalence of cancers of various types and the serious effects it can have, more effective treatments, especially those with fewer adverse side effects than currently available forms of treatment, are needed.

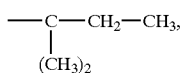
## SUMMARY OF THE INVENTION

This invention relates to pharmaceutical compositions useful in treating cancer in a mammal. The pharmaceutical compositions of the present invention comprise two compounds: a first compound which is paclitaxel, taxotere or a modified taxane or taxoid analog and a second compound, which is a compound of Formula I:

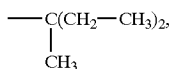


Formula I is discussed in detail below. Some examples of compounds of Formula I are specifically presented herein. For example, compounds of Formula I can be those in which R<sup>1</sup> and R<sup>2</sup> are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 1-isoleucyl or 2-tert-butylglycyl; D is thiazolidinylcarbonyl, 3,4-dehydroprolyl or prolyl; E is prolyl, thiazolidinyl-4-carbonyl, homoprolyl, hydroxyprolyl or 3,4-dehydroprolyl; and K is a substituted amino moiety having the formula R<sup>5</sup>-N-R<sup>6</sup>, wherein R<sup>5</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub>-alkoxy and R<sup>6</sup> is a monovalent radical such as (1)- or (2)-adamantyl; (CH<sub>2</sub>)<sub>v</sub>-phenyl with v=1; α,α-dimethylbenzyl; a C<sub>1</sub>-C<sub>12</sub> linear or branched hydroxyalkyl group, such as —C(CH<sub>3</sub>)<sub>2</sub>—CH<sub>2</sub>—CH<sub>2</sub>—OH, also referred to as 3-hydroxy-1,1-dimethylpropyl; a C<sub>3</sub>-C<sub>10</sub> cycloalkyl group, such as bicyclo[3.3.0]octa-1-yl, 1-methylcyclopentyl or 1-methylcyclohexyl; or a C<sub>1</sub>-C<sub>12</sub> linear or branched alkyl group, such as

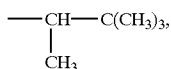
—C(CH<sub>3</sub>)<sub>3</sub>, also referred to as tert-butyl;



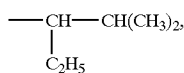
also referred to as 1,1-dimethylpropyl;



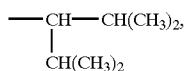
also referred to as 1-methyl-1-ethylpropyl;



also referred to as (S)- or (R)-1-methyl-2,2-dimethylpropyl;



also referred to as (S)- or (R)-1-ethyl-2-methylpropyl;



also referred to as 1-isopropyl-2-methylpropyl; or

—C(CH<sub>3</sub>)<sub>2</sub>—CH(CH<sub>3</sub>)<sub>2</sub>, also referred to as 1,1-dimethyl-2-methylpropyl;

—CH(CH<sub>3</sub>)<sub>2</sub>, also referred to as isopropyl;

—CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, sec-butyl [(S) or (R)]; or

—CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)<sub>2</sub>, also referred to as 1,2-dimethylpropyl.

Each compound is present in the pharmaceutical composition in an effective amount. The pharmaceutical composition can include one or more of each type of compound (e.g., one or more of the first type of compound, such as paclitaxel or paclitaxel and taxotere and one or more compounds of Formula I).

This invention also relates to methods of treating cancer in a mammal in which the pharmaceutical compounds described herein are used. In the method of the present invention, the two compounds are administered in the pharmaceutical composition or as individual/separate compounds which are given sufficiently close in time to have the desired effect.

It has been discovered that, surprisingly the combination of paclitaxel, taxotere or a modified taxane or taxoid analog as described herein and a compound having Formula I as described herein provides enhanced or therapeutically synergistic anticancer effects in vivo. For purposes of this invention, two drugs are considered therapeutically synergistic if a combination regimen produces a significantly better tumor cell kill than the best constituent when it is administered alone at optimal or maximum tolerated doses. Differences in tumor cell kill less than half a decade are not considered significant.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1A-1D depict compounds i-xvii, as examples of compounds of Formula I.

The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawings.

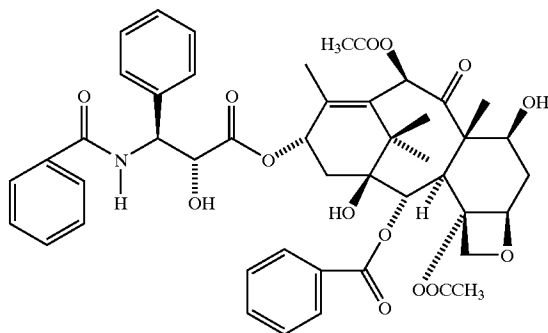
## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to pharmaceutical compositions useful in treating cancer in a mammal. The pharmaceutical composition of the present invention comprises two compounds: a first compound which is paclitaxel, taxotere or a modified taxane or taxoid analog and a second compound of Formula I as further described below. Each compound is present in the pharmaceutical composition in an effective amount. One or more of each type of compound can be present in the pharmaceutical composition or administered in the present method. As used herein the term "an effective amount" refers to an amount sufficient to elicit the desired biological response. In the instant invention, the

desired biological response is inhibition (partial or total) of formation of a tumor or a hematological malignancy, reversal of the development of a solid tumor or other malignancy or prevention or reduction of its further progression.

### PACLITAXEL, TAXOTERE OR A MODIFIED TAXANE OR TAXOID ANALOG

Paclitaxel (Taxol®), which is one example of a first compound of the pharmaceutical composition, is a diterpene isolated from the bark of the Western (Pacific) yew, *Taxus brevifolia* and is representative of a class of therapeutic agent having a taxane ring system. The formula for paclitaxel is:



Paclitaxel and its analogs have been produced by partial synthesis from 10-deacetylbaccatin III, a precursor obtained from yew needles and twigs, and by total synthesis. See Holton, et al., *J. Am. Chem. Soc.* 116:1597-1601 (1994) and Nicolaou, et al., *Nature* 367:630 (1994). Paclitaxel has been demonstrated to possess antineoplastic activity. More recently, it was shown that the antitumor activity of paclitaxel is due to a promotion of microtubule polymerization. See Kumar, N., *J. Biol. Chem.* 256:10435-10441 (1981); Rowinsky, et al., *J. Natl. Cancer Inst.* 82:1247-1259 (1990); and Schiff, et al., *Nature* 277:655-667 (1979). Paclitaxel has now demonstrated efficacy in several human tumors in clinical trials. See McGuire, et al., *Ann. Int. Med.* 111:237-279 (1989); Holmes, et al., *J. Natl. Cancer Inst.* 83:1797-1805 (1991); Kohn et al., *J. Natl. Cancer Inst.* 86:18-24 (1994); and Kohn, et al., *American Society for Clinical Oncology* 12 (1993). Paclitaxel is available from Bristol-Myers Squibb Company, New York, N.Y. by the registered tradename Taxol®.

The first compound in the pharmaceutical composition is typically paclitaxel (Taxol®), taxotere or a modified taxane or taxoid analog. The modified taxane or taxoid analogs are those compounds having a taxane ring bearing modified side chains. A number of these analogs have improved properties, such as greater water solubility and stability than that of naturally occurring paclitaxel. For example, RPR109881 is a new oral and iv active taxoid analog under development by Rhone-Poulenc Rhorer and currently in Phase I Clinical Trials. These analogs are known to those of skill in the art and are disclosed, for example, in U.S. Pat. Nos. 5,278,324; 5,272,171; 5,254,580; 5,250,683; 5,248,796; and 5,227,400, the disclosures of which are incorporated herein by reference. Taxotere can be prepared by the method in WO 93/18210, the disclosure of which is incorporated herein by reference. In particular embodiments, the first compound in the pharmaceutical composition is paclitaxel or taxotere.

### COMPOUNDS OF FORMULA I

A number of short peptides with significant activity as inhibitors of cell growth have been isolated from the Indian

Ocean sea hare *Dolabella auricularia* (Bai, et al., *Biochem. Pharmacology*, 40: 1859-1864 (1990); Beckwith et al., *J. Natl. Cancer Inst.*, 85: 483-488 (1993) and references cited therein). These include Dolastatins 1-10 (U.S. Pat. No. 4,816,444, issued to Pettit et al.) and Dolastatin-15 (European Patent Application No. 398558). Dolastatin-15, for example, markedly inhibits the growth of the National Cancer Institute's P388 lymphocytic leukemia cell line, a strong predictor of efficacy against various types of human malignancies. This compound, however, is present only in trace quantities in the sea hare and is difficult to isolate, expensive to synthesize and suffers from poor aqueous solubility.

The compounds of Formula I are derivatives of Dolastatin-15, which overcome the above-mentioned disadvantages of Dolastatin-15 while retaining antineoplastic activity or exhibiting greater antineoplastic activity than the natural product. The Dolastatin-15 derivatives of Formula I, which are employed in combination with paclitaxel, taxotere or a modified taxane or taxoid analog in the present invention, can be synthesized, as described herein and in related copending application U.S. Ser. No. 08/472,453, filed Jun. 7, 1995, the teachings of which are incorporated herein in their entirety.

The Dolastatin-15 derivatives of Formula I generally comprise L-amino acids, but they can also contain one or more D-amino acids, as described in related copending application U.S. Ser. No. 08/472,453 filed on Jun. 7, 1995. The compounds of Formula I can also be present as salts with physiologically-compatible acids, such as, but not limited to, hydrochloric acid, citric acid, tartaric acid, lactic acid, phosphoric acid, methanesulfonic acid, acetic acid, formic acid, maleic acid, fumaric acid, malic acid, succinic acid, malonic acid, sulfuric acid, L-glutamic acid, L-aspartic acid, pyruvic acid, mucic acid, benzoic acid, glucuronic acid, oxalic acid, ascorbic acid and acetylglycine.

For purposes of the present invention, the term "monovalent radical" is intended to mean an electrically neutral molecular fragment capable of forming one covalent bond with a second neutral molecular fragment. Monovalent radicals include the hydrogen atom, alkyl groups (e.g. methyl, ethyl, propyl and tert-butyl groups), cycloalkyl groups, hydroxy alkyl groups, adamantyl groups, halogen atoms (e.g. fluorine, chlorine and bromine atoms), aryl groups (e.g. phenyl, benzyl and naphthyl groups) and alkoxy groups (e.g. methoxy and ethoxy groups). Two monovalent radicals on adjacent sigma-bonded atoms can also form a pi bond between the adjacent atoms. Two monovalent radicals may also be linked together, for example, by a polymethylene unit to form a cyclic structure. For example, the unit  $-N(R)R'$ , wherein R and R' are monovalent radicals, can, together with the nitrogen atom, form a heterocyclic ring. In addition, two monovalent radicals bonded to the same atom can also form a divalent radical, such as an alkylidene group, for example, a propylidene group, or an oxygen atom.

More specifically, for the compounds of Formula I:

R<sup>1</sup> is alkyl, such as C<sub>1</sub>-C<sub>3</sub>; cycloalkyl, such as cyclopropyl; alkylsulfonyl, such as C<sub>1</sub>-C<sub>3</sub>; fluoroalkyl, such as fluoroethyl, difluoroethyl, fluoroisopropyl; aminosulfonyl which may be substituted by alkyl, such as methyl; R<sup>2</sup> is hydrogen; alkyl, such as C<sub>1</sub>-C<sub>3</sub>; fluoroalkyl, such as fluoroethyl, difluoroethyl, fluoroisopropyl; cycloalkyl, such as cyclopropyl;

R<sup>1</sup>-N-R<sup>2</sup> together may be a pyrrolidino or piperidino residue;

A is a valyl, isoleucyl, leucyl, allo-isoleucyl, 2,2-dimethylglycyl, 2-cyclopropylglycyl,

## 5

2-cyclopentylglycyl, 3-tert-butylalanyl, 2-tert-butylglycyl, 3-cyclohexylalanyl, 2-ethylglycyl, 2-cyclohexylglycyl, norleucyl or norvalyl residue;

B is a N-alkyl-valyl, -norvalyl, -leucyl, -isoleucyl, -2-tert-butylglycyl, -3-tert-butylalanyl, -2-ethylglycyl, -2-cyclopropylglycyl, -2-cyclopentylglycyl, norleucyl or -2-cyclohexylglycyl residue where N-alkyl is preferably N-methyl or N-ethyl;

D is a prolyl, homoprolyl, hydroxypropyl, 3,4-dehydropropyl, 4-fluoropropyl, 3-methylpropyl, 4-methylpropyl, 5-methylpropyl, azetidine-2-carbonyl, 3,3-dimethylpropyl, 4,4-difluoropropyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;

E is a prolyl, homoprolyl, hydroxypropyl, 3,4-dehydropropyl, 4-fluoropropyl, 3-methylpropyl, 4-methylpropyl, 5-methylpropyl, azetidine-2-carbonyl, 3,3-dimethylpropyl, 4,4-difluoropropyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;

F and G are independently selected from the group consisting of prolyl, homoprolyl, hydroxypropyl, thiazolidinyl-4-carbonyl, 1-aminopentyl-1-carbonyl, valyl, 2-tert-butylglycyl, isoleucyl, leucyl, 3-cyclohexylalanyl, phenylalanyl, N-methylphenylalanyl, tetrahydroquinolyl-2-histidyl, 1-aminoinidyl-1-carbonyl, 3-pyridylalanyl, 2-cyclohexylglycyl, norleucyl, norvalyl, neopentylglycyl, tryptophanyl, glycyl, 2,2-dimethylglycyl alanyl, 9-alanyl and 3-naphthylalanyl residues;

X is hydrogen, alkyl (such as C<sub>1</sub>-C<sub>5</sub>), cycloalkyl (such as C<sub>3</sub>-C<sub>7</sub>), -CH<sub>2</sub>-cyclohexyl or arylalkyl (such as benzyl or phenethyl);

s, t and u are independently 0 or 1; and

K is hydroxy, alkoxy (such as C<sub>1</sub>-C<sub>4</sub>), phenoxy, benzyloxy or a substituted or unsubstituted amino moiety.

In addition, the compounds of Formula I can be present as a salt thereof with physiologically tolerated acids.

One subclass of compounds of this invention includes compounds of Formula I wherein R<sup>1</sup>-N-R<sup>2</sup> is a pyrrolidiny or piperidinyl residue.

Another subclass of compounds of this invention includes compounds of Formula I wherein K is an amino moiety of the formula R<sup>5</sup>-N-R<sup>6</sup>, wherein:

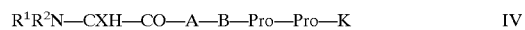
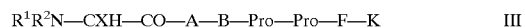
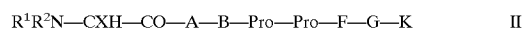
R<sup>5</sup> is hydrogen, or hydroxy, or C<sub>1-7</sub> alkoxy, or benzyloxy, or phenoxy or C<sub>1-12</sub> linear or branched hydroxyalkyl, such as 3-hydroxy-1,1-dimethylpropyl, or C<sub>1-7</sub> linear or branched alkyl (which may be substituted by one or more fluoro atoms), or C<sub>3-10</sub>-cycloalkyl, such as bicyclo[3.3.0]octa-1-yl, 1-methylcyclopentyl or 1-methylcyclohexyl; or benzyl (which may be substituted by up to three substituents which may independently be CF<sub>3</sub>, nitro, C<sub>1-7</sub> alkylsulfonyl, C<sub>1-4</sub> alkoxy, phenoxy, benzyloxy, halogen, C<sub>1-4</sub>-alkyl, cyano, hydroxy, N(CH<sub>3</sub>)<sub>2</sub>, COOMe, COOEt, COOiPr, or COONH<sub>2</sub>);

R<sup>6</sup> is hydrogen, or C<sub>1-12</sub> linear or branched alkyl (which may be substituted by one or more fluoro atoms), or C<sub>1-12</sub> linear or branched hydroxyalkyl, such as 3-hydroxy-1,1-dimethylpropyl, or C<sub>3-10</sub>-cycloalkyl, such as bicyclo[3.3.0]octa-1-yl, or 1-methylcyclopentyl or 1-methylcyclohexyl; or -(CH<sub>2</sub>)<sub>v</sub>-C<sub>3-7</sub>-cycloalkyl (v=0,1,2, or 3), or norephedryl, or norpseudoephedryl, or quinolyl, or pyrazyl, or -CH<sub>2</sub>-benzimidazolyl, or (1)-adamantyl, or (2)-adamantyl- -CH<sub>2</sub>-adamantyl, or alpha-methylbenzyl, or alpha-dimethylbenzyl, or -(CH<sub>2</sub>)<sub>v</sub>-phenyl

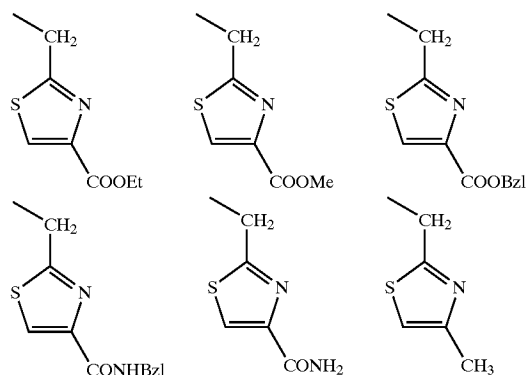
## 6

(v=0,1,2, or 3; which may be substituted by up to two substituents which may independently be CF<sub>3</sub>, nitro, C<sub>1-7</sub> alkylsulfonyl, C<sub>1-4</sub> alkoxy, phenoxy, benzyloxy, halogen, C<sub>1-4</sub>-alkyl which may form a cyclic system, cyano, hydroxy, N(CH<sub>3</sub>)<sub>2</sub>, COOMe, COOEt, COOiPr, or COONH<sub>2</sub>), or -(CH<sub>2</sub>)<sub>m</sub>-naphthyl (m=0 or 1); or -(CH<sub>2</sub>)<sub>w</sub>-benzhydryl (w=0,1, or 2); or biphenyl or picolyl or benzothiazolyl or benzoisothiazolyl or benzopyrazolyl or benzoxazolyl or -(CH<sub>2</sub>)<sub>m</sub>-fluorenyl (m=0 or 1); or pyrimidyl or -(CH<sub>2</sub>)<sub>m</sub>-indanyl (m=0 or 1); or -(CH<sub>2</sub>CH<sub>2</sub>O)<sub>y</sub>-CH<sub>3</sub> (y=0,1,2,3,4, or 5), or -(CH<sub>2</sub>CH<sub>2</sub>O)<sub>y</sub>-CH<sub>2</sub>CH<sub>3</sub> (y=0,1,2,3,4, or 5), or NH-C<sub>6</sub>H<sub>5</sub> (which may be substituted by up to two substituents which may independently be CF<sub>3</sub>, nitro, C<sub>1-7</sub> alkylsulfonyl, C<sub>1-4</sub> alkoxy, halogen, C<sub>1-4</sub> alkyl which may form a cyclic system, cyano, hydroxy, COOMe, COOEt, COOiPr, or COONH<sub>2</sub>), or -NCH<sub>3</sub>-C<sub>6</sub>H<sub>5</sub> or -NH-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub> or -NCH<sub>3</sub>-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub> or 5-membered heteroaryl which may be substituted by up to two substituents which may independently be CF<sub>3</sub>, nitro, thiomethyl, thioethyl, C<sub>3-6</sub>-cycloalkyl, -CH<sub>2</sub>-COOEt, C<sub>3-4</sub>-alkylene group forming a bicyclic system with the heterocycle, phenyl; or -CHR<sup>7</sup>-5-membered heteroaryl (which may be substituted by up to two substituents which may independently be CF<sub>3</sub>, nitro, cyano, halogen, COOMe, COOEt, COOiPr, CONH<sub>2</sub>, C<sub>1-4</sub>-alkyl, C<sub>1-4</sub>-alkoxy, phenyl, benzyl, naphthyl, or C<sub>1-7</sub>-alkylsulfonyl [R<sup>7</sup>=hydrogen, linear or branched C<sub>1-5</sub> alkyl, benzyl; or R<sup>7</sup> and R<sup>5</sup> together form a group -(CH<sub>2</sub>)<sub>3</sub>- or -(CH<sub>2</sub>)<sub>4</sub>-).

This subclass includes compounds of Formula I wherein s, t and u are independently 0 or 1; R<sup>1</sup>, R<sup>2</sup> and X are lower alkyl, A is a lower alkyl amino acid, B is a N-loweralkylated lower alkyl amino acid; D,E,F,G and K are as previously defined. With the foregoing in mind, three sets of such compounds can thus be depicted by the following formulas II, III, and IV:

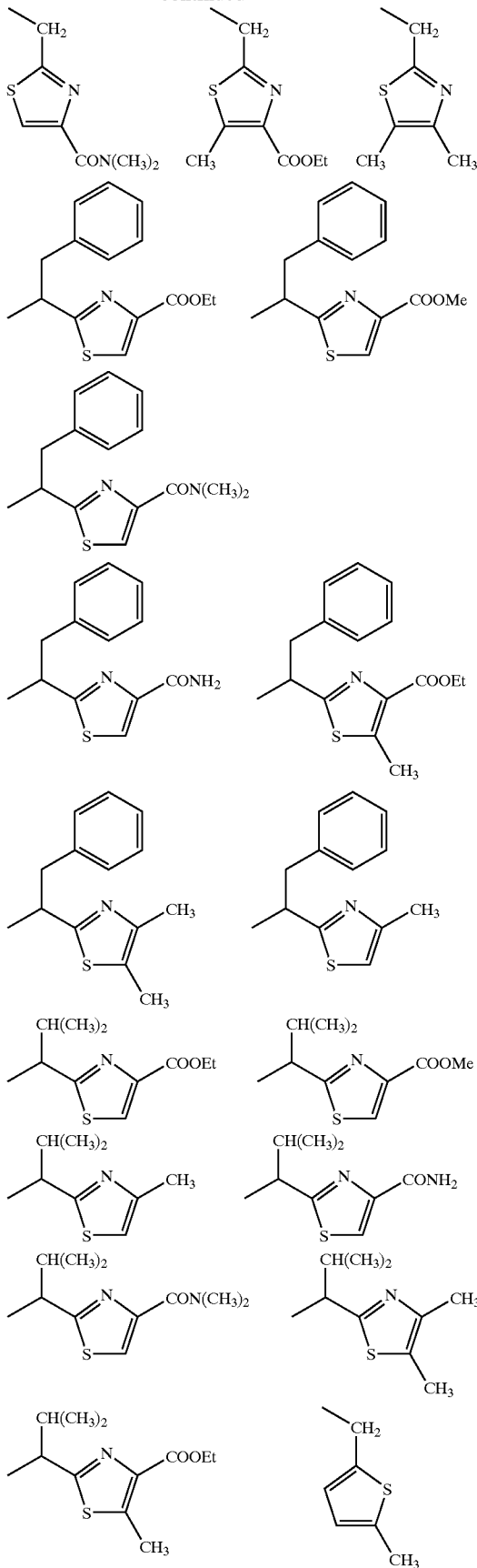


-CHR<sup>7</sup>-5-membered heteroaryl may, for example, be represented by one of the following residues:



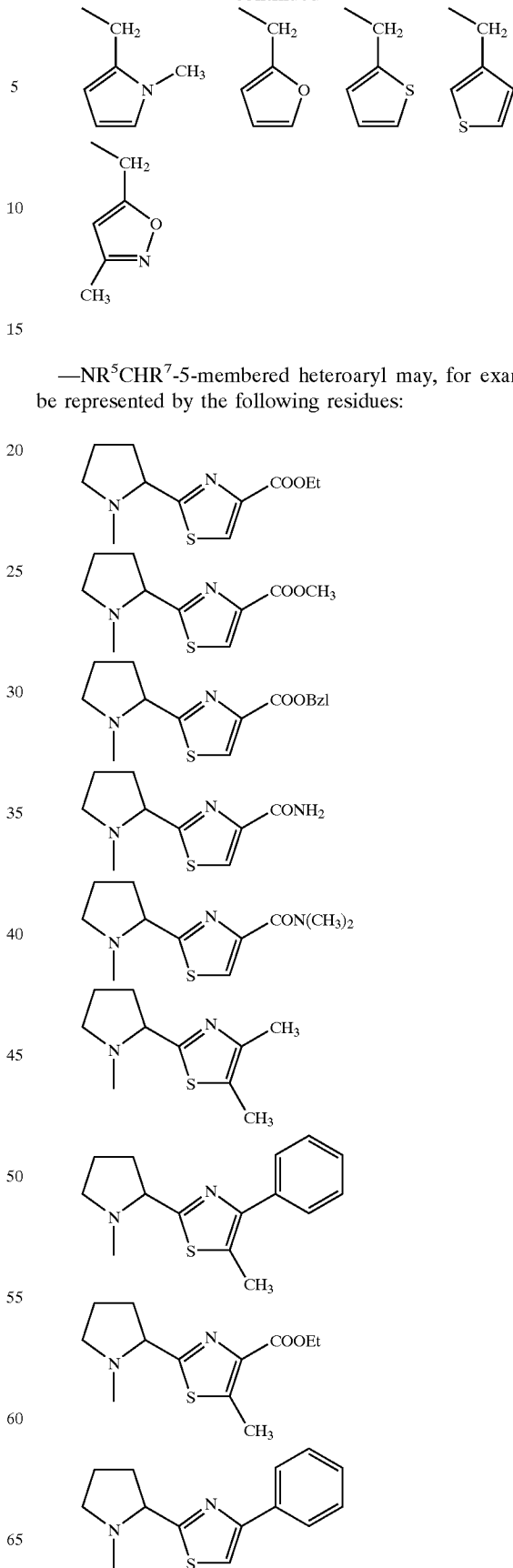
7

-continued

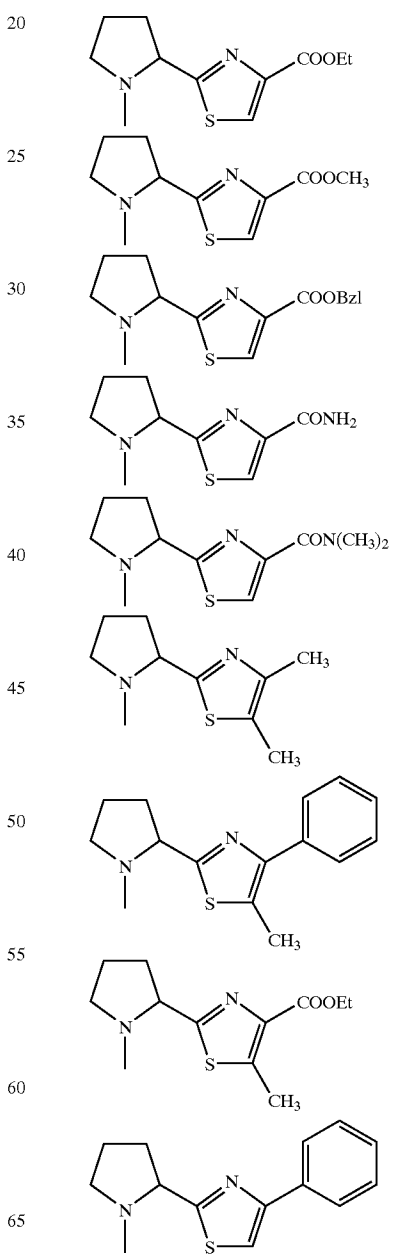


8

-continued



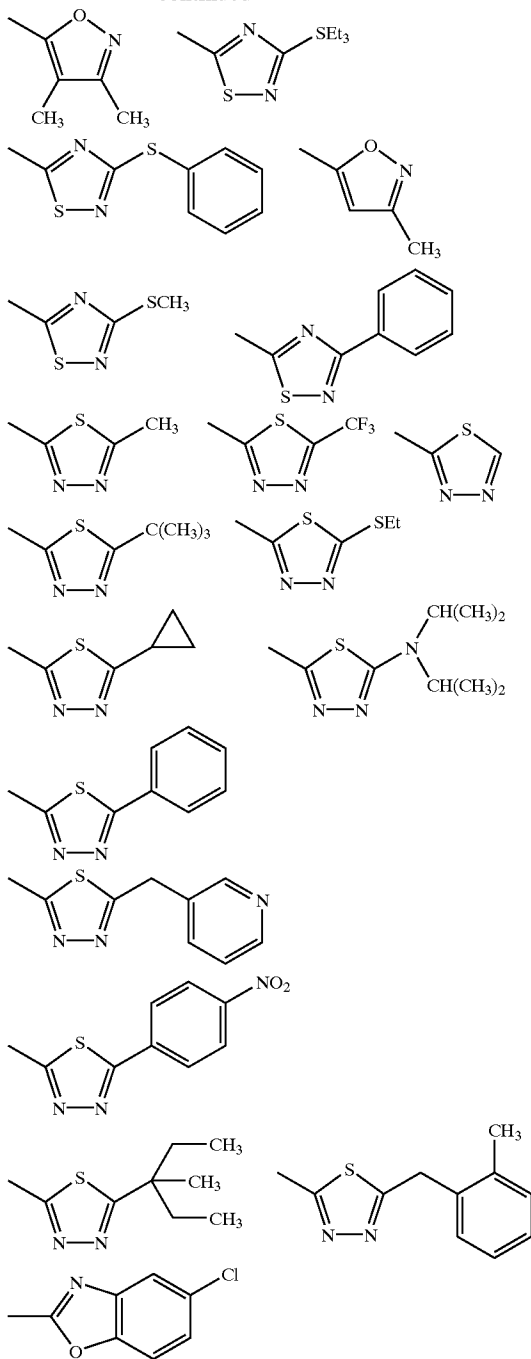
—NR<sup>5</sup>CHR<sup>7</sup>-5-membered heteroaryl may, for example, be represented by the following residues:



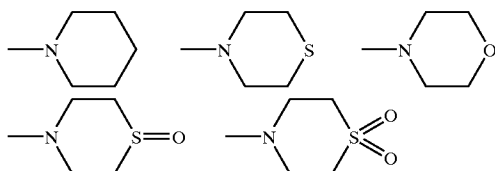


11

-continued

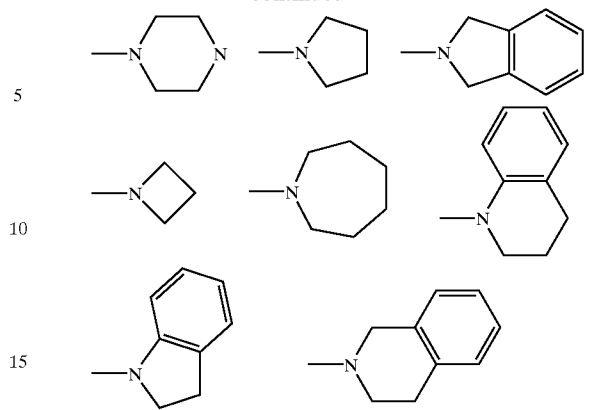


In another subclass of compounds of this invention R<sup>1</sup>-N-R<sup>6</sup> together may form structures selected from the group consisting of:



12

-continued



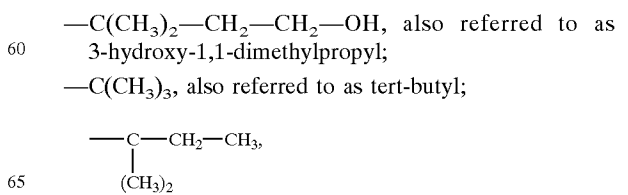
Still another subclass of compounds of this invention includes, for example, compounds of Formula I wherein s, t and u are 1 and K is a hydroxy, alkoxy, phenoxy or benzyloxy moiety.

Yet another subclass of compounds of this invention includes, for example, compounds of Formula I wherein s and t are 1, u is 0 and K is a hydroxy, alkoxy, phenoxy or benzyloxy moiety.

Another subclass of compounds of this invention includes, for example, compounds of Formula I wherein s is 1, t and u are 0 and K is a hydroxy, alkoxy, phenoxy or benzyloxy moiety.

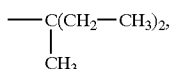
In particular embodiments, the second compound in the pharmaceutical composition of the invention is a compound of Formula I in which R<sup>1</sup> and R<sup>2</sup> are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 1-isoleucyl or -2-tert-butylglycyl; D is prolyl, thiazolidinyl-4-carbonyl or 3,4 dehydroprolyl; E is prolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted or unsubstituted amino moiety having the formula R<sup>5</sup>-N-R<sup>6</sup>.

In a further embodiment, the second compound in the pharmaceutical composition is a compound of Formula I in which R<sup>1</sup> and R<sup>2</sup> are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 1-isoleucyl or 2-tert-butylglycyl; D is prolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R<sup>5</sup>-N-R<sup>6</sup> wherein R<sup>5</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkoxy and R<sup>6</sup> is a C<sub>1</sub>-C<sub>12</sub> linear or branched alkyl group or a C<sub>1</sub>-C<sub>12</sub> linear or branched hydroxyalkyl group represented, for example, by the following monovalent radicals:

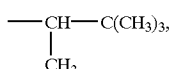


13

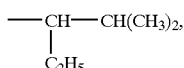
also referred to as 1,1-dimethyl propyl;



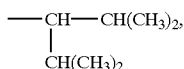
also referred to as 1-methyl-1-ethyl propyl;



also referred to as (S)- or (R)-1-methyl-2,2-dimethyl propyl;



also referred to as (S)- or (R)-1-ethyl-2-methyl propyl;



also referred to as 1-isopropyl-2-methyl butyl; or

---C(CH<sub>3</sub>)<sub>2</sub>---CH(CH<sub>3</sub>)<sub>2</sub>, also referred to as 1,1-dimethyl-2-methyl propyl

---CH(CH<sub>3</sub>)<sub>2</sub>, also referred to as isopropyl

---CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, also referred to as sec-butyl, (S)--- or (R)---

---CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)<sub>2</sub>, also referred to as 1,2-dimethylpropyl.

In another embodiment, the second compound in the pharmaceutical composition of the invention is a compound of Formula I in which R<sup>1</sup> and R<sup>2</sup> are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 1-isoleucyl or 2-tert-butylglycyl; D is prolyl, thiazolidinyl-4-carbonyl, 3,4-dehydroprolyl; E is prolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R<sup>5</sup>---N---R<sup>6</sup> wherein R<sup>5</sup> is hydrogen or C<sub>1</sub>---C<sub>4</sub> alkoxy and R<sup>6</sup> is a monovalent radical such as a C<sub>3</sub>---C<sub>10</sub> cycloalkyl group (e.g. cyclobutyl, cyclopentyl, cyclohexyl, or 1-methylcyclopentyl, or 1-methylcyclohexyl or bicyclo [3.3.0]octa-1-yl); a (1)- or (2)-adamantyl group; (CH<sub>2</sub>)<sub>v</sub>-phenyl with v=1 or α,α-dimethylbenzyl.

In a further embodiment, the second compound in the pharmaceutical composition of the invention is a compound of Formula I in which R<sup>1</sup> and R<sup>2</sup> are each methyl; X is isopropyl; s is 1; t and u are each 0; A is valyl; B is N-methylvalyl; D is prolyl; E is prolyl; and K is a substituted amino moiety having the formula R<sup>5</sup>---N---R<sup>6</sup> wherein R<sup>5</sup> is benzyl and R<sup>6</sup> is hydrogen. This compound corresponds to compound (xvii) depicted in FIG. 1D. The results of the use of compound (xvii) of Formula I, in combination with paclitaxel are presented in Tables 1-4.

The pharmaceutical compositions of the present invention may optionally contain a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known to those who are skilled in the art. The choice of a carrier will be determined in part by the particular compounds in the combination, as well as by the particular method used to administer the pharmaceutical composition. Accordingly,

14

there is a wide variety of suitable formulations of the pharmaceutical compositions of the present invention. For example, paclitaxel (Taxol®) is available as a sterile non-pyrogenic solution which includes polyoxyethylated castor oil (Cremophor® EL) and dehydrated alcohol, USP.

In another aspect, the present invention comprises a method for partially or totally inhibiting formation of, or otherwise treating (e.g., reversing or inhibiting the further development of) solid tumors (e.g., tumors of the lung, breast, colon, prostate, bladder, rectum, or endometrium) or hematological malignancies (e.g., leukemias, lymphomas) in a mammal, for example, a human, by administering to the mammal an effective amount of a first compound which is paclitaxel, taxotere or a modified taxane or taxoid analog and administering an effective amount of a second compound, which is a compound of Formula I.

The two compounds are administered in combination according to the invention. The term in combination in this context means that the drugs are given either simultaneously or sequentially. If given sequentially, one of the two compounds is usually detectable in the serum of the subject at the onset of administration of the other compound. In one embodiment, a compound of Formula I is administered first, followed by administration of the above described first compound, such as paclitaxel. In a specific embodiment, paclitaxel is administered about one hour after administration of a compound of Formula I. Alternatively, the first compound and the second compound can be administered simultaneously, or the first compound could be administered first, followed by administration of a second compound, which is a compound of Formula I.

The first and the second compounds may be administered alone or with a pharmaceutically accepted carrier or diluent appropriate for the desired route of administration. Administration can be by any of the means which are conventional for pharmaceutical, preferably oncological, agents, including oral and parenteral means such as subcutaneously, intravenously, intramuscularly, intraperitoneally, nasally or rectally. Such pharmaceutical compositions may also contain other therapeutically active ingredients.

The dosage administered to the mammal, such as a human, includes a combination of an effective amount of a compound of Formula I and an effective amount of paclitaxel, taxotere or modified taxane or taxoid analog, as described herein. For a particular condition or method of treatment, the dosage can be determined empirically, using known methods, and will depend upon factors such as the biological activity, mechanism of action, cross resistance, overlapping toxicity and toxicity profile of the particular compounds employed; the means of administration; the age, health and body weight of the recipient; the nature and extent of the symptoms; the frequency of treatment; the administration of other therapies; and the effect desired.

A typical daily dose of the compounds of Formula I will be from about 5 to about 250 milligrams per kilogram of body weight by oral administration and from about 1 to about 100 milligrams per kilogram of body weight by parenteral administration. A typical daily dose of paclitaxel, taxotere or a modified taxane or taxoid analog will generally be from 5 to about 250 milligrams per kilogram.

The first and the second compounds of the present invention can be administered in conventional solid or liquid pharmaceutical administration forms, for example, uncoated or (film)coated tablets, capsules, powders, granules, suppositories or solutions. These are produced in a conventional manner. The active substances can for this purpose be processed with conventional pharmaceutical aids such as

15

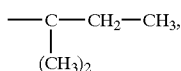
tablet binders, fillers, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, sustained release compositions, anti-oxidants and/or propellant gases (cf. H. Sücker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1978). The administration forms obtained in this way typically contain from about 1 to about 90% by weight of the active substance.

The compounds of Formula I are described in detail above. In a particular embodiment, the method of the invention uses a compound of Formula I in which R<sup>1</sup> and R<sup>2</sup> are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 1-isoleucyl or 2-tert-butylglycyl; D is prolyl, thiazolidinyl-4-carbonyl or 3,4-dehydroprolyl; E is prolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted or unsubstituted amino moiety having the formula R<sup>5</sup>—N—R<sup>6</sup>.

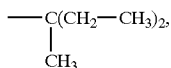
In a further embodiment, the method of the invention uses a compound of Formula I in which R<sup>1</sup> and R<sup>2</sup> are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 1-isoleucyl or 2-tert-butylglycyl; D is prolyl, thiazolidinyl-4-carbonyl or 3,4-dehydroprolyl; E is prolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R<sup>5</sup>—N—R<sup>6</sup> wherein R<sup>5</sup> is hydrogen or C<sub>1</sub>—C<sub>4</sub> alkoxy and R<sup>6</sup> is a C<sub>1</sub>—C<sub>12</sub> linear or branched alkyl group or C<sub>1</sub>—C<sub>12</sub> linear or branched hydroxyalkyl group represented, for example, by the following monovalent radicals:

—C(CH<sub>3</sub>)<sub>2</sub>—CH<sub>2</sub>—CH<sub>2</sub>—OH, also referred to as 3-hydroxy-1,1-dimethylpropyl;

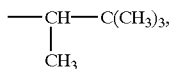
—C(CH<sub>3</sub>)<sub>3</sub>, also referred to as tert-butyl;



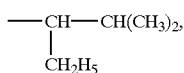
also referred to as 1,1-dimethyl propyl;



also referred to as 1-methyl-1-ethyl propyl;

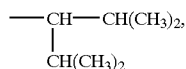


also referred to as (S)- or (R)-1-methyl-2,2-dimethyl propyl;



16

also referred to as (S)- or (R)-1-ethyl-2-methyl propyl;



also referred to as 1-isopropyl-2-methyl butyl; or

—C(CH<sub>3</sub>)<sub>2</sub>—CH(CH<sub>3</sub>)<sub>2</sub>, also referred to as 1,1-dimethyl-2-methyl propyl

—CH(CH<sub>3</sub>)<sub>2</sub>, also referred to as isopropyl

—CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, also referred to as sec-butyl, (S)— or (R)—

—CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)<sub>2</sub>, also referred to as 1,2-dimethylpropyl.

In another embodiment, the method of the invention uses a compound of Formula I in which R<sup>1</sup> and R<sup>2</sup> are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 1-isoleucyl or 2-tert-butylglycyl; D is prolyl, thiazolidinyl-4-carbonyl 3,4-dehydroprolyl; E is prolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R<sup>5</sup>—N—R<sup>6</sup> wherein R<sup>5</sup> is hydrogen or C<sub>1</sub>—C<sub>4</sub> alkoxy and R<sup>6</sup> is a monovalent radical such as a C<sub>3</sub>—C<sub>10</sub> cycloalkyl group (e.g. cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl, 1-methylcyclohexyl or bicyclo[3.3.0]octa-1-yl); a (1)- or (2)-adamantyl group; (CH<sub>2</sub>)<sub>v</sub>-phenyl with v=1 or α,α-dimethylbenzyl.

In a further embodiment, the method of the invention uses a compound of Formula I in which R<sup>1</sup> and R<sup>2</sup> are each methyl; X is isopropyl; s is 1; t and u are each 0; A is valyl; B is N-methylvalyl; D is prolyl; E is prolyl; and K is a substituted amino moiety having the formula R<sup>5</sup>—N—R<sup>6</sup> wherein R<sup>5</sup> is benzyl and R<sup>6</sup> is hydrogen. This compound corresponds to compound (xvii) depicted in FIG. 1D. The results of the use of compound (xvii) of Formula I, in combination with paclitaxel are presented in Tables 1—4.

#### SYNTHETIC METHODS

The compounds of Formula I can be prepared by known methods of peptide synthesis such as those described herein and, in U.S. patent application Ser. No. 08/470,453 filed Jun. 7, 1995, the teachings of which are incorporated herein by reference. The peptides can be assembled sequentially from individual amino acids or by linking suitable small peptide fragments. In sequential assembly, the peptide chain is extended stepwise, starting at the C-terminus, by one amino acid per step. In fragment coupling, fragments of different lengths can be linked together, and the fragments can also be obtained by sequential assembly from amino acids or by fragment coupling of still shorter peptides.

In both sequential assembly and fragment coupling it is necessary to link the units by forming an amide linkage, which can be accomplished via a variety of enzymatic and chemical methods. The methods described herein for formation of peptidic amide linkages, are also suitable for the formation of non-peptidic amide linkages.

Chemical methods for forming the amide linkage are described in detail in standard references on peptide chemistry, including Müller, *Methoden der organischen Chemie* Vol. XV/2, 1—364, Thieme Verlag, Stuttgart, (1974); Stewart and Young, *Solid Phase Peptide Synthesis*, 31—34 and 71—82, Pierce Chemical Company, Rockford, Ill. (1984); Bodanszky et al., *Peptide Synthesis*, 85—128, John

Wiley & Sons, New York, (1976); *Practice of Peptide Synthesis*, M. Bodansky, A. Bodansky, Springer-Verlag, 1994 and other standard works in peptide chemistry. Preferred methods include the azide method, the symmetric and mixed anhydride method, the use of in situ generated or preformed active esters, the use of urethane protected N-carboxy anhydrides of amino acids and the formation of the amide linkage using coupling reagents, such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), pivaloyl chloride, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI), n-propane-phosphonic anhydride (PPA), N,N-bis (2-oxo-3-oxazolidinyl)amido phosphoryl chloride (BOP-Cl), bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBrop), diphenylphosphoryl azide (DPPA), Castro's reagent (BOP, PyBop), O-benzotriazolyl-N,N,N',N'-tetramethyluronium salts (HBTU), O-azabenzotriazolyl-N,N,N',N'-tetramethyluronium salts (TATU), diethylphosphoryl cyanide (DEPCN), 2,5-diphenyl-2,3-dihydro-3-oxo-4-hydroxythiophene dioxide (Steglich's reagent; HOTDO), and 1,1'-carbonyldiimidazole (CDI). The coupling reagents can be employed alone or in combination with additives such as N,N-dimethyl-4-aminopyridine (DMAP), N-hydroxy-benzotriazole (HOBT), N-hydroxybenzotriazine (HOBT), N-hydroxysuccinimide (HOSu) or 2-hydroxypyridine.

Although the use of protecting groups is generally not necessary in enzymatic peptide synthesis, reversible protection of reactive groups not involved in formation of the amide linkage is necessary for both reactants in chemical synthesis. Three conventional protective group techniques typically used for chemical peptide synthesis are: the benzyloxycarbonyl (Z), the t-butoxycarbonyl (Boc) and the 9-fluorenylmethoxycarbonyl (Fmoc) techniques. Identified in each case is the protective group on the  $\alpha$ -amino group of the chain-extending unit. A detailed review of amino-acid protective groups is given by Müller, *Methoden der organischen Chemie* Vol. XV/1, pp 20-906, Thieme Verlag, Stuttgart (1974).

The units employed for assembling the peptide chain can be reacted in solution, in suspension or by a method similar to that described by Merrifield in *J. Amer. Chem. Soc.* 85 (1963) 2149. In one method, peptides are assembled sequentially or by fragment coupling using the Z, Boc or Fmoc protective group technique, with one of the reactants in the Merrifield technique being bonded to an insoluble polymeric support (also called resin hereinafter). This typically entails assembling the peptide sequentially on the polymeric support using the Boc or Fmoc protective group technique, with the growing peptide chain covalently bonded at the C terminus to the insoluble resin particles. This procedure allows the removal of reagents and by-products by filtration, eliminating the need to recrystallize intermediates.

The protected amino acids can be linked to any suitable polymer, which must be insoluble in the solvents used and have a stable physical form which permits filtration. The polymer must contain a functional group to which the first protected amino acid can be covalently attached. A wide variety of polymers are suitable for this purpose, for example, cellulose, polyvinyl alcohol, polymethacrylate, sulfonated polystyrene, chloromethylated styrene/divinylbenzene copolymer (Merrifield resin), 4-methylbenzhydrylamine resin (MBHA-resin), phenylacetamidomethyl resin (Pam-resin), p-benzyloxybenzyl-alcohol-resin, benzhydryl-amine-resin (BHA-resin), 4-(hydroxymethyl)-benzoyl-oxymethyl-resin, the resin of

Breipohl et al. (*Tetrahedron Letters* 28 (1987) 565; supplied by BACHEM), 4-(2,4-dimethoxyphenylaminomethyl) phenoxy resin (supplied by Novabiochem) or o-chlorotriptyl-resin (supplied by Biohellas).

Solvents suitable for peptide synthesis include any solvent which is inert under the reaction conditions, for example, water, N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, dichloromethane (DCM), 1,4-dioxane, tetrahydrofuran (THF), N-methyl-2-pyrrolidone (NMP) and mixtures of these solvents.

Peptide synthesis on the polymeric support can be carried out in a suitable inert organic solvent in which the amino acid derivatives and starting materials employed are soluble. Particularly useful solvents are, for example, DMF, DCM, NMP, acetonitrile, DMSO and mixtures thereof, due to their resin swelling properties.

Following synthesis, the peptide is removed (commonly referred to as cleaved) from the polymeric support. The conditions under which this cleavage is accomplished are well known in the art of peptide synthesis and depend in part on the type of resin employed. The cleavage reactions most commonly used are acid- or palladium-catalyzed, the acid catalyzed cleavage being conducted in, for example, liquid anhydrous hydrogen fluoride, anhydrous trifluoroacetic acid, and acetic acid/dichloromethane/trifluoroethanol mixtures. The palladium-catalyzed cleavage can be carried out in THF or THF-DCM-mixtures in the presence of a weak base such as morpholine. Certain protecting groups are also cleaved off under these conditions.

Partial deprotection of the peptide may also be necessary prior to certain derivatization reactions. For example, peptides dialkylated at the N-terminus can be prepared either by coupling the appropriate N,N-di-alkylamino acid to the peptide in solution or on the polymeric support or by reductive alkylation of the resin-bound peptide in DMF/1% acetic acid with NaCNBH<sub>3</sub> and the appropriate aldehyde or by hydrogenation of the peptide in solution in the presence of aldehyde or ketone and Pd/C.

The various non-naturally occurring amino acids as well as the various non-amino acid moieties disclosed herein may be obtained from commercial sources or synthesized from commercially-available materials using methods known in the art. For example, amino acid building blocks with R<sup>1</sup> and R<sup>2</sup> moieties can be prepared according to E. Wuensch, Huben Weyl, *Methoden der organischen Chemie* Vol. XV/1, p. 306, Thieme Verlag, Stuttgart (1974) and literature cited therein. Peptides with gamma- or delta-lactam bridges can be prepared by incorporating the appropriate lactam-bridged dipeptide units (R. Freidinger, *J. Org. Chem.* (1982) 104-109) into the peptide chain. Peptides with thiazole-, oxazol-, thiazolin- or oxazolin-containing dipeptide building blocks can be prepared by incorporating the appropriate dipeptidic units (P. Jouin et al., *Tetrahedron Letters* (1992), pp. 2087-2810; P. Wipf et al., *Tetrahedron Letters* (1992), pp. 907-910; W. R. Tully, *J. Med. Chem.* (1991), p 2065; *Synthesis* (1987), p 235) into the peptide chain.

The following procedures are intended to illustrate methods useful for preparation of compounds of Formula I. When applicable, amino acids are abbreviated using the known three letter codes. Other meanings used are: Me<sub>2</sub>Val=N,N-dimethylvaline, MeVal=N-methylvaline, TFA=trifluoroacetic acid, Ac=acetic acid, Bu=butyl, Et=ethyl, Me=methyl, Bzl=benzyl, Nal=3-naphthylalanine, Cha=3-cyclohexylalanine, Npg=neopentyl glycine, Abu=2-amino butyryl, Dab=2,4-diaminobutyryl, iPr=isopropyl

## GENERAL SYNTHETIC PROCEDURES

I. Compounds of Formula I of the present invention are either synthesized by classical solution synthesis using standard Z- and Boc-methodology as described above or by standard methods of solid-phase synthesis on a completely automatic model 431A synthesizer supplied by APPLIED BIOSYSTEMS. The apparatus uses different synthetic cycles for the Boc and Fmoc protective group techniques.

In the case of solid phase synthesis, the N,N-dialkylpent- or hexapeptide acids are liberated from the solid support and further coupled with the corresponding C-terminal amines in solution. BOP-Cl and PyBrop were used as reagents for coupling of the amino acid following the N-methylamino acids. The reaction times were correspondingly increased. For reductive alkylation of the N-terminus, the peptide-resin was deprotected at the N terminus and then reacted with a 3-fold molar excess of aldehyde or ketone in DMF/1% acetic acid with addition of 3 equivalents of NaCNBH<sub>3</sub>. After the reaction was complete (negative Kaiser test) the resin was washed several times with water, isopropanol, DMF and dichloromethane.

In solution synthesis, the use of either Boc-protected amino acid NCAs (N-tert-butyloxycarbonyl-amino acid-N-carboxy-anhydrides), Z-protected amino acid NCAs (N-benzyloxycarbonyl-amino acid-N-carboxy-anhydrides), or the use of pivaloylchloride as condensing agent respectively is most advantageous for coupling of the amino acid following the N-methylamino acids. Reductive alkylation of the N terminus can, for example, be achieved by reaction of the N-terminally deprotected peptides or amino acids with the corresponding aldehydes or ketones using NaCNBH<sub>3</sub> or hydrogen, Pd/C.

a) Synthetic Cycle for the Boc Protective Group Technique:

1.	30% trifluoroacetic acid in DCM	1 × 3 min
2.	50% trifluoroacetic acid in DCM	1 × 1 min
3.	DCM washing	
4.	5% diisopropylethylamine in DCM	5 × 1 min
5.	5% diisopropylethylamine in NMP	1 × 1 min
6.	NMP washing	5 × 1 min
7.	Addition of preactivated protected amino acid (DCC and 1 equivalent of HOBT in NMP/DCM); Peptide coupling (1st part)	1 × 30 min
8.	Addition of DMSO to the reaction mixture until it contains 20% DMSO by volume; Peptide coupling (2nd part)	1 × 16 min
9.	Addition of 3.8 equivalents of diisopropylethylamine to the reaction mixture; Peptide coupling (3rd part)	1 × 7 min
10.	DCM washing	3 × 1 min
11.	If conversion is incomplete, repetition of coupling (back to 6)	
12.	10% acetic anhydride, 5% diisopropylethylamine in DCM	1 × 2 min
13.	10% acetic anhydride in DCM	1 × 4 min
14.	DCM washing	4 × 1 min
15.	Back to 1.	

BOP-Cl and PyBrop were used as reagents for coupling of the amino acid following N-methylamino acids. The reaction times were correspondingly increased. In solution synthesis, the use of either Boc-protected amino acid NCAs (N-tert-butyloxycarbonyl-amino acid-N-carboxy-anhydrides) or Z-protected amino acids NCAs respectively is most advantageous for this type of coupling.

b) Synthetic Cycle for the Fmoc Protective Group Technique:

1.	DMF washing	1 × 1 min
2.	20% piperidine in DMF	1 × 4 min
3.	20% piperidine in DMF	1 × 16 min
4.	DMF washing	5 × 1 min
5.	Addition of the preactivated protected amino acid (activation by 1 equivalent of TBTU and 5 equivalents of DIPEA in DMF); Peptide coupling	1 × 61 min
6.	DMF washing	3 × 1 min
7.	If conversion is incomplete, repetition of coupling (back to 5)	
8.	10% acetic anhydride in DMF	1 × 8 min
9.	DMF washing	3 × 1 min
10.	Back to 2.	

BOP-Cl and PyBrop were used as reagents for coupling on the amino acid following the N-methylamino acids. The reaction times were correspondingly increased.

II. Reductive Alkylation of the N-terminus

The peptide-resin prepared in Ia or Ib above was deprotected at the N-terminus (steps 2–4 in Ib or 1–6 in Ia) and then reacted with a 3-fold molar excess of aldehyde or ketone in DMF/1% acetic acid with addition of 3 equivalents of NaCNBH<sub>3</sub>. After reaction was complete (negative Kaiser test) the resin was washed several times with water, isopropanol, DMF and dichloromethane.

III. Workup of the Peptide-resins Obtained as in Ia and II

The peptide-resin was dried under reduced pressure and transferred into a reaction vessel of a TEFLON HF apparatus (supplied by PENINSULA). Addition of a scavenger, for example, anisole (1 ml/g of resin), and in the case of tryptophan-containing peptides of a thiol to remove the indolic formyl group, for example, ethanedithiol (0.5 ml/g of resin), was followed by condensing in hydrogen fluoride (10 ml/g of resin) while cooling with liquid N<sub>2</sub>. The mixture was allowed to warm to 0° C. and stirred at this temperature for 45 minutes. The hydrogen fluoride was then stripped off under reduced pressure, and the residue was washed with ethyl acetate in order to remove remaining scavenger. The peptide was extracted with 30% acetic acid and filtered, and the filtrate was lyophilized.

IV. Work-up of the Peptide-resins Obtained as in Ib and II

The peptide-resin was dried under reduced pressure and then subjected to one of the following cleavage procedures, depending on the amino acid composition (Wade, Tregear, Howard Florey Fmoc Workshop Manual, Melbourne 1985).

	TFA	Scavenger	Reaction time
1.	95%	5% water	1.5 h
2.	95%	5% ethanedithiol/ anisole (1:3)	1.5 h

The suspension of the peptide-resin in the suitable TFA mixture was stirred at room temperature for the stated time and then the resin was filtered off and washed with TFA and DCM. The filtrate and the washings were concentrated, and the peptide was precipitated by addition of the diethyl ether. After cooling in an ice bath, the precipitate was filtered off, taken up in 30% acetic acid and lyophilized.

V. When an o-chlorotrityl-resin (supplied by Biohellas) is used, the suspension of the peptide-resin in an acetic acid/trifluoroethanol/dichloromethane mixture (1:1:3) is stirred at

room temperature for 1 h. The resin is then filtered off with suction and thoroughly washed with the cleavage solution. The combined filtrates are concentrated in vacuo and treated with water. The precipitated solid is removed by filtration or centrifugation, washed with diethyl ether and dried under reduced pressure.

#### VI. Purification and Characterization of the Peptides

Purification was carried out by gel chromatography (SEPHADEX G-10, G-15/10% HOAc, SEPHADEX LH20/MeOH) medium pressure chromatography (stationary phase: HD-SIL C-18, 20–45 micron, 100 Angstrom; mobile phase: gradient with A=0.1% TFA/MeOH, B=0.1% TFA/water) or preparative HPLC (stationary phase: water Delta-Pak C-18, 15 micron, 100 Angstrom; mobile phase: gradient with A=0.1% TFA/MeOH, B=0.1% TFA/water).

The purity of the resulting products was determined by analytical HPLC (stationary phase: 100 2.1 mm VYDAC C-18, 51, 300 Angstrom; mobile phase:

acetonitrile-water gradient, buffered with 0.1% TFA, 40° C).

Characterization was by amino acid analysis and fast atom bombardment mass spectroscopy.

### SPECIFIC SYNTHETIC PROCEDURES

#### EXAMPLE 1A

##### N,N-Dimethyl-Val-Val-N-methyl-Val-Pro-Pro-Val-Phe-NH<sub>2</sub>

1.98 g of Fmoc-RINK-resin (substitution 0.46 mmol/g), corresponding to a batch size of 0.84 mmol, were reacted as in Ib above with 1.26 mmol each of

Fmoc-Phe-OH

Fmoc-Val-OH

Fmoc-Pro-OH

Fmoc-Pro-OH

Fmoc-N-methyl-Val-OH

Fmoc-Val-OH

Fmoc-Val-OH

The amino acid following the N-methyl amino acid was coupled on with PyBrop as coupling reagent. After the iterative synthetic cycles were completed, the peptide-resin underwent N-terminal deprotection (steps 2–4 in Ib), and was further reacted with aqueous formaldehyde solution as in II and then dried under reduced pressure. The resulting resin was subjected to TFA cleavage as in IV. The crude product (590 mg) was purified by gel filtration (SEPHADEX-LH-20). The yield was 295 mg.

#### EXAMPLE 1A

Example 1 can also be prepared via classical solution phase methodology. The synthesis of N,N-dimethyl-Val-Val-N-methyl-Val-Pro-Pro-Val-Phe-NH<sub>2</sub> and its associated intermediates is described in the following paragraph.

##### a) Z-MeVal-Pro-Ome

66.25 g (250 mmol) of Z-MeVal-OH were dissolved in 250 ml of dry dichloromethane. After addition of 36.41 ml (262.5 mmol) of triethylamine, the reaction mixture was cooled to -25° C. and 32.37 ml (262.5 mmol) pivaloyl chloride were added. After stirring for 2.5 hours, 41.89 g (250 mmol) of H-Pro-Ome-HCl in 250 ml of dichloromethane, neutralized with 36.41 ml (262.5 mmol) triethylamine at 0° C., were added to the reaction mixture. Stirring was continued for 2h at -25° C. and overnight at room temperature. The reaction mixture was diluted with

dichloromethane and thoroughly washed with saturated aqueous NaHCO<sub>3</sub> solution (3×), water (1×), 5% citric acid (3×) and saturated NaCl solution. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness. The residue (91.24 g) was stirred with petroleum ether overnight and filtered. 62.3 g of product were obtained.

##### b) H-MeVal-Pro-Ome

48.9 g (130 mmol) Z-MeVal-Pro-Ome were dissolved in 490 ml of methanol. After addition of 10.9 ml (130 mmol) concentrated hydrochloric acid and 2.43 g of 10% palladium/charcoal, the reaction mixture was hydrogenated. Filtration and evaporation to dryness yielded 36.43 g of product.

##### c) Z-Val-MeVal-Pro-Ome

18.1 g (65 mmol) of H-MeVal-Pro-Ome, 21.6 g (78 mmol) Z-Val-N-carboxyanhydride and 22.8 ml (130 mmol) diisopropylethylamine were stirred in 110 ml of DMF at 40° C. for 2 days. After evaporation of DMF, dichloromethane was added and the organic phase washed with saturated aqueous NaHCO<sub>3</sub> solution (3×), water (1×) 5% citric acid (3×) and saturated NaCl solution. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness. The product (29.3 g) was obtained as a viscous oil.

##### d) H-Val-MeVal-Pro-Ome

29.3 g (61.6 mmol) of Z-Val-MeVal-Pro-Ome were dissolved in 230 ml of methanol. After addition of 1.15 g of 10% palladium/charcoal, the reaction mixture was hydrogenated. Filtration and evaporation to dryness yielded 21.96 g of product.

##### e) Z-Val-Val-MeVal-Pro-Ome

15.29 g (61 mmol) of Z-Val-OH and 21.96 g (61 mmol) of H-Val-MeVal-Pro-Ome were dissolved in 610 ml of dichloromethane and cooled to 0° C. After addition of 8.16 mol(73.2 mmol) of N-methylmorpholine, 2.77 g (20.3 mmol) of HOBt and 11.74 g (61 mmol) of EDCI, the reaction mixture was stirred overnight at room temperature, diluted with dichloromethane and thoroughly washed with saturated aqueous NaHCO<sub>3</sub> solution (3×), water (1×), 5% citric acid (3×) and saturated NaCl solution. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness to yield 31.96 g of the product.

##### f) Z-Val-Val-MeVal-Pro-OH

31.96 g (57 mmol) of Z-Val-Val-MeVal-Pro-Ome were dissolved in 250 ml of methanol. 102.6 ml of a 1N LiOH solution was added and the mixture stirred overnight at room temperature. After addition of 500 ml of water, the aqueous phase was washed three times with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness yielding 30.62 g of the desired product as a white solid.

##### g) Z-Val-Val-MeVal-Pro-Pro-Val-Phe-NH<sub>2</sub>

25 g (43.3 mmol) of Z-Val-Val-MeVal-Pro-OH and 15.59 g (43.3 mmol) of H-Pro-Val-Phe-NH<sub>2</sub> were suspended in 430 ml of dry dichloromethane. After cooling to 0° C., 5.81 ml (52 mmol) N-methylmorpholine, 1.97 g (15 mmol) of HOBt and 8.33 g (43.3 mmol) of EDCI were added and the reaction mixture stirred overnight at room temperature. The solvents were evaporated, the residue dissolved in 640 ml of dichloromethane and thoroughly washed with saturated aqueous NaHCO<sub>3</sub> solution (4×), water (1×), 5% citric acid (3×) and saturated NaCl solution. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness to yield 33.04 g of the product. The crude product was chromatographed on a silica gel column with 20% MeOH/hexane. 18.32 g of the desired product were obtained.

## 23

b) N,N-Dimethyl-Val-Val-MeVal-Pro-Pro-Val-Phe-NH<sub>2</sub>

18.32 g of Z-Val-Val-MeVal-Pro-Pro-Val-Phe-NH<sub>2</sub> were dissolved in 80 ml of methanol. 0.4 g of 10% palladium/carbon were added under nitrogen atmosphere and the reaction mixture hydrogenated at room temperature for 4 hours. After addition of 6.22 ml (81.24 mmol) of a 37% aqueous formaldehyde solution, hydrogenation was continued for 5 hours. Filtration and evaporation of the solvent gave rise to 15.6 g of crude product. Further purification was achieved by dissolving the peptide in water, adjusting the pH to 2 and extracting the aqueous phase three times with ethyl acetate. The aqueous phase was then adjusted to pH 8–9 and extracted four times with ethyl acetate. The organic phase was washed with water and dried over sodium sulfate, filtered and evaporated to yield 11.3 g of purified product as a white powder. The compound was characterized by fast atom bombardment mass spectrometry ([M+H]<sup>+</sup>=797).

## EXAMPLE 2A

N,N-Dimethyl-Val-Val-NMe-Val-Pro-[1-[thiazol-(2)-yl]-2-phenyl]-ethylamide

4.11 g of Fmoc-Pro-p-alkoxybenzyl-alcohol-resin (substitution 0.73 mmol/g), corresponding to a batch size of 3 mmol, were reacted as in Ib with 4.5 mmol each of

Fmoc-N-MeVal-OH

Fmoc-Val-OH

Fmoc-Val-OH

The amino acid following the N-methylamino acid was in this case reacted with double coupling using PyBrop or Bop-Cl with increased reaction times. After the synthesis was complete, the peptide-resin underwent N-terminal deprotection (Steps 2–4 in Ib), and was further reacted with aqueous formaldehyde solution as in II and then dried under reduced pressure. The resin obtained in this way was subjected to TFA cleavage as in IV. The crude product (750 mg) was employed directly for the next coupling. 100 mg of this compound were reacted with 45 mg of (S)-2-[1-amino-2-phenylethyl]thiazole and 230 mg of PyBop with the addition of 192 microliters of DIPEA in DMF at room temperature for 2 days. The reaction mixture was purified by gel chromatography (SEPHADEX LH-20, methanol) and the product fractions were combined. 83 mg of product were obtained.

## EXAMPLE 1B

Me<sub>2</sub>Val-Val-MeVal-Pro-Pro-NHCH(CH<sub>3</sub>)<sub>2</sub>

a) Z-MeVal-Pro-OMe

66.25 g (250 mmol) Z-MeVal-OH were dissolved in 250 ml dry dichloromethane. After addition of 36.41 ml (262.5 mmol) triethylamine, the reaction mixture was cooled to –25° C. and 32.27 ml (262.5 mmol) pivaloyl chloride were added. After stirring for 2.5 h, 41.89 g (250 mmol) H-Pro-OMe·HCl in 250 ml dichloromethane, neutralized with 36.41 ml (262.5 mmol) triethylamine at 0° C., were added to the reaction mixture. Stirring continued for 2 h at –25° C. and overnight at room temperature. The reaction mixture was diluted with dichloromethane and thoroughly washed with saturated aqueous NaHCO<sub>3</sub> solution (3×), water (1×), 5% citric acid (3×) and saturated NaCl solution. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness. The residue (91.24 g) was stirred with petroleum ether overnight and filtered. 62.3 g of product were obtained.

## 24

b) H-MeVal-Pro-OMe

48.9 g (130 mmol) Z-MeVal-Pro-OMe were dissolved in 490 ml methanol. After addition of 10.9 ml (130 mmol) concentrated hydrochloric acid and 2.43 g 10% Palladium/charcoal, the reaction mixture was hydrogenated. Filtration and evaporation to dryness yielded 36.43 g of the product.

c) Z-Val-MeVal-Pro-OMe

18.1 g (65 mmol) H-MeVal-Pro-OMe, 21.6 g (78 mmol) Z-Val-N-carboxyanhydride and 22.8 ml (130 mmol) diisopropylethylamine were stirred in 110 ml DMF at 40° C. for 2 d. After evaporation of DMF, dichloromethane was added and the organic phase washed with saturated aqueous NaHCO<sub>3</sub> solution (3×), water (1×), 5% citric acid (3×) and saturated NaCl solution. The organic phase was dried over sodium sulfate and evaporated to dryness. The product (29.3 g) was obtained as a viscous oil.

d) H-Val-MeVal-Pro-OMe

29.3 g (61.6 mmol) of Z-Val-MeVal-Pro-OMe were dissolved in 230 ml methanol. After addition of 1.15 g 10% Palladium/charcoal, the reaction mixture was hydrogenated. Filtration and evaporation to dryness yielded 21.96 g of the product.

e) Z-Val-Val-MeVal-Pro-OMe

15.29 g (61 mmol) Z-Val-OH and 21.96 g (61 mmol) H-Val-MeVal-Pro-OMe were dissolved in 610 ml dichloromethane and cooled to 0° C. After addition of 8.16 ml (73.2 mmol) N-Methylmorpholine, 2.77 g (20.3 mmol) HOBt and 11.74 g (61 mmol) EDCI, the reaction mixture was stirred overnight at room temperature, diluted with dichloromethane and thoroughly washed with saturated aqueous NaHCO<sub>3</sub> solution (3×), water (1×), 5% citric acid (3×) and saturated NaCl solution. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness to yield 31.96 g of the product.

f) Z-Val-Val-MeVal-Pro-OH

31.96 g (57 mmol) Z-Val-Val-MeVal-Pro-OMe were dissolved in 250 ml methanol. 102.6 ml of a 1 N LiOH solution was added and the mixture stirred overnight at room temperature. After addition of 500 ml water, the aqueous phase was washed three times with ethyl acetate, adjusted to pH 2 at 0° C. and extracted three times with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness yielding 30.62 g of the desired product as a white solid.

g) Z-Val-Val-MeVal-Pro-Pro-NHCH(CH<sub>3</sub>)<sub>2</sub>

2 g (3.35 mmol) Z-Val-Val-MeVal-Pro-OH and 0.664 g (3.35 mmol) H-Pro-NHCH(CH<sub>3</sub>)<sub>2</sub> were dissolved in 34 ml of dry dichloromethane. After cooling to 0° C., 1.35 ml (12.1 mmol) N-methylmorpholine, 0.114 g (0.84 mmol) HOBt and 0.645 g (3.35 mmol) EDCI were added and the reaction mixture stirred overnight at room temperature. 80 ml dichloromethane were added and the organic phase thoroughly washed with saturated aqueous NaHCO<sub>3</sub> solution (3×), water (1×), 5% citric acid (3×) and saturated NaCl solution (1×). The organic phase was dried over sodium sulfate, filtered and evaporated to dryness to yield 1.96 g of the product which was used in the next reaction without further purification.

h) Me<sub>2</sub>Val-Val-MeVal-Pro-Pro-NHCH(CH<sub>3</sub>)<sub>2</sub>

1.96 g Z-Val-Val-MeVal-Pro-Pro-NHCH(CH<sub>3</sub>)<sub>2</sub> were dissolved in 11 ml methanol. 0.054 g 10% Pd/C were added under nitrogen atmosphere and the reaction mixture hydrogenated at room temperature for 4 h. After addition of 0.86 ml (11.24 mmol) of a 37% aqueous formaldehyde solution and 0.281 g 10% Pd/C, hydrogenation was continued for 5 h. Filtration and evaporation of the solvent gave rise to 2.77

g of crude product. Further purification was achieved by dissolving the peptide in water, adjusting the pH to 2 and extracting the aqueous phase three times with ethyl acetate. The aqueous phase was then adjusted to pH 8–9 and extracted four times with dichloromethane. The organic phase was dried over sodium sulfate, filtered and evaporated to yield 1.37 g of purified product as a white foam. The compound was further purified using medium pressure liquid chromatography (10–50% A in 10 min.; 50–90% A in 320 min.). Fractions containing the product were combined, lyophilized, redissolved in water and the pH adjusted to 9 with 1 N LiOH. After extraction with dichloromethane, the organic phase was dried over sodium sulfate, filtered and evaporated to dryness. Lyophilization led to 500 mg of pure product, which was characterized by fast atom bombardment mass spectrometry ( $[M+H]^+=593$ ).

#### EXAMPLE 2B

$\text{Me}_2\text{Val-Val-MeVal-Pro-Pro-NHC}(\text{CH}_3)_3$

a)  $\text{Z-Val-Val-MeVal-Pro-Pro-NHC}(\text{CH}_3)_3$

2 g (3.35 mmol) Z-Val-Val-MeVal-Pro-OH and 0.692 g (3.35 mmol) H-Pro-NHC( $\text{CH}_3$ )<sub>3</sub> were dissolved in 34 ml of dry dichloromethane. After cooling to 0° C., 1.35 ml (12.1 mmol) N-methylmorpholine, 0.114 g (0.84 mmol) HOBt and 0.645 g (3.35 mmol) EDCI were added and the reaction mixture stirred overnight at room temperature. 80 ml dichloromethane were added and the organic phase thoroughly washed with saturated aqueous  $\text{NaHCO}_3$  solution (3x), water (1x), 5% citric acid (3x) and saturated NaCl solution (1x). The organic phase was dried over sodium sulfate, filtered and evaporated to dryness to yield 1.8 g of the product which was used in the next reaction without further purification.

b)  $\text{Me}_2\text{Val-Val-MeVal-Pro-Pro-NHC}(\text{CH}_3)_3$

1.8 g Z-Val-Val-MeVal-Pro-Pro-NHC( $\text{CH}_3$ )<sub>3</sub> were dissolved in 10 ml methanol. 0.045 g 10% Pd/C were added under nitrogen atmosphere and the reaction mixture hydrogenated at room temperature for 4 h. After addition of 0.86 ml (11.24 mmol) of a 37% aqueous formaldehyde solution and 0.252 g 10% Pd/C, hydrogenation was continued for 5 h. Filtration and evaporation of the solvent gave rise to 1.82 g of crude product. The compound was further purified using medium pressure liquid chromatography (10–50% A in 10 min.; 50–90% A in 320 min.). Fractions containing the product were combined, lyophilized, redissolved in water and the pH adjusted to 9 with 1 N LiOH. After extraction with dichloromethane, the organic phase was dried over sodium sulfate and evaporated to dryness. Lyophilization led to 547 mg of pure product, which was characterized by fast atom bombardment mass spectrometry ( $[M+H]^+=607$ ).

#### EVALUATION OF BIOLOGICAL ACTIVITY

##### In vivo Methodology

The combination of a compound of Formula I and paclitaxel, taxotere or a modified taxane or taxoid analog was further tested in various preclinical assays for in vivo activity, which are indicative of clinical utility. The P388 (ascites model), LX-1, CX-1 and PC-3 (human tumor xenograft models for lung, colon and prostate) tumor models are all suitable for use in this invention.

In general, any dosing regimen which appears to provide an acceptable level of antitumor activity for both agents is

suitable. Any acceptable method of drug administration can be used in the combination therapy of this invention and can be determined using techniques well known to those of skill in the art. In addition, the drugs can be administered either simultaneously or sequentially, in any order.

#### P388 MODEL

The P388 tumor model employs a murine lymphocytic leukemia cell line (See Schabel et al., *Pharmac. Ther. A*, 1:411–435). The P388 tumor cells used in this invention, were harvested from donor mice by peritoneal lavage at day 7 post transplant.  $1 \times 10^6$  P388 tumor cells were then implanted intraperitoneally in a volume of 0.5 ml in mice.

A typical dosing regimen includes initiation of treatment approximately one day post transplant followed by treatment on days 5 and 9 post transplant. Generally the compounds of Formula I are administered intravenously (i.v.) and the paclitaxel, taxotere or modified taxane or taxoid analog is administered intraperitoneally (i.p.).

Therapeutic results of the combinations of the invention against P388 cells, are presented in terms of increase in lifespan reflected by the relative median survival time (MST) of treated (T) versus control (C) group (survival period for untreated mice is generally in the range of 11 to 13 days) and is represented as %T/C values. According to the National Cancer Institute guidelines a %T/C in the range or 128–190% indicates a drug with moderate to good activity. In addition, the Net log Cell Kill is used to compare efficacy of different schedules and combinations, and is calculated as follows:

$$\text{Net log Cell Kill} = \frac{[(T - C) - \text{duration of treatment}] \times 0.332}{\text{Doubling Time}}$$

Where,

Doubling Time=time required for control tumors to double once (0.4 days)

T and C=the median survival time (days) for the control (C) and treated (T) mice.

Duration of treatment with drug 0.332=Derived constant  
A positive Net log Cell Kill number indicates that fewer tumor cells are present at the end of treatment. A negative number indicates that the tumor was still growing during treatment.

#### EXAMPLE 3

##### Combination Treatment Using Compound (xvii) and Paclitaxel in the P388 Tumor Model

$1 \times 10^6$  P388 tumor cells were transplanted intraperitoneally in a volume of 0.5 ml in mice. Treatment was initiated approximately 1 day later followed by treatment on both day 5 and day 9, post transplant. Compound (xvii) was administered IV while paclitaxel was administered IP. Compound (xvii) was administered at either 20, 40 or 60 mg/kg and paclitaxel at either 10, 20 or 30 mg/kg. The dosing was sequential with compound (xvii) being administered first followed by paclitaxel one hour later.

#### RESULTS

The results from Example 3 are shown in Table 1. The data in Table 1 shows that single drug treatment resulted in an optimal %T/C of 175% for compound (xvii) corresponding to a Net log Cell Killing (NICK) of 0.66 when administered intravenously at a dose of 60 mg/kg and an optimal

%T/C of 183% corresponding to a NICK of 1.33 for paclitaxel when administered intraperitoneally at a dose of 10 mg/kg. For combination drug treatment the data of Table 1 show that the combination of 60 mg/kg (xvii) and 20 mg/kg of paclitaxel resulted in a significant increase in life span (P Value less than 0.001, as determined by the Mann-Whitney Test) and an optimal %T/C value of 242% corresponding to a NICK of 5.98 with 38% of the animals surviving more than 60 days.

HUMAN TUMOR XENOGRAFTS MODEL

Human tumors from lung (LX-1), colon (CX-1) and prostate (PC-3) which had been grown in athymic nude mice were transplanted (xenografted) into new recipient mice, as is well known in the art. The transplanted tumor fragments were approximately 50 mg in size. The day of transplantation was designated as day 0. The combination therapy of the present invention was evaluated for anti-tumor efficacy following administration to the xenograft-bearing mice.

Combination therapy was accomplished by intravenous administration of both drugs. The Q2dx3; 5, 12 and 19 injection schedule was followed with paclitaxel being administered one hour after Compound (xvii). In other words, treatment consisted of 3 cycles, starting on days 5, 12 and 19 post tumor implantation. One cycle of treatment consisted of treatment every other day for a total of three times. The optimal dose for single dose administration of both Compound (xvii) and paclitaxel used in the LX-1 and CX-1 types of human xenograft models tested, can be found in Tables 2-3, with no optimal dose determined with the PC-3 model.

Tumor diameters and body weights were measured twice weekly. Tumor volumes were calculated using the diameters measured with Vernier calipers, and the formula:

$$(\text{length} \times \text{width}^2) / 2 = \text{mg of tumor weight}$$

Mean tumor weights (MTW) were calculated for each treatment group, and T/C values determined for each group relative to the untreated control tumors.

Results are also presented as Net log Cell Kill and are calculated as follows:

$$\text{Net log Cell Kill} = \frac{[(T - C) - \text{duration of treatment}] \times 0.332}{\text{Doubling Time}}$$

T and C=The median days required for the control and treated tumors to reach a specified tumor size, in this instance 2000 mm<sup>3</sup>.

Doubling Time=Time required for control tumors to double in size.

0.332=Derived constant

EXAMPLE 4

Combination Treatment Using Compound 103793 and Paclitaxel in the LX-1 Human Tumor Xenograft Model

The Q2dx3; 5, 12 and 19 dosing regimen described above was used in this example. Paclitaxel was administered IV one hour after Compound (xvii) was administered IV. The optimal single dose of both paclitaxel and Compound (xvii) can be determined from Table 2.

TABLE 1

DOSE RESPONSE OF COMPOUND (xvii) WITH AND WITHOUT PACLITAXEL AGAINST THE P388 IN VIVO TUMOR MODEL							
DRUGS		%		% 60			
(xvii) IV	Paclitaxel IP	Toxic Death	% T/C	Net Log Cell Kill	Day Cures	Total # Animals	
Dose (mg/kg)							
	0	30	8	204	2.99	3	36
	0	20	0	175	0.66	4	24
	0	10	0	183	1.33		24
	60	0	0	175	0.66		42
	40	0	0	158	-0.66	2	42
	20	0	0	158	-0.66		42
	60	30	25	217	3.98	25	24
	60	20	4	242	5.98	38	24
	60	10	0	204	2.99		24
	40	30	21	212	3.65	8	24
	40	20	0	212	3.65	12	24
	40	10	0	183	1.33		24
	20	30	8	217	3.98	25	24
	20	20	0	217	3.98	14	22
	20	10	0	183	1.33	4	24

Q4Dx3; 1 Paclitaxel injected one hour after (xvii)

EXAMPLE 5

Combination Treatment Using Compound 103793 and Paclitaxel in the CX-1 Human Tumor Xenograft Model

The Q2dx3; 5, 12 and 19 dosing regimen described above was used in this example. Paclitaxel was administered IV one hour after Compound (xvii) was administered IV. The optimal single dose of both paclitaxel and Compound (xvii) can be determined from Table 3.

EXAMPLE 6

Combination Treatment Using Compound 103793 and Paclitaxel in the PC-3 Human Tumor Xenograft Model

The Q2dx3; 5, 12 and 19 dosing regimen described above was used in this example. Paclitaxel was administered IP one hour after Compound (xvii) was administered IV. The optimal single dose of both paclitaxel and Compound (xvii) was not determined.

RESULTS

The results obtained using the Human Xenograft Model to assess anti-tumor efficacy of the combination therapy of the present invention are presented in Tables 2-4. The data presented represents results from preliminary experiments. The data in Table 2 show that the optimal combination of compound (xvii) and paclitaxel was 15 mg/kg and 10 mg/kg respectively, in the LX-1 model. The combination resulted in some regressions and tumor growth delay. However, the same combination schedule in the CX-1 model did not result in any advantage over the single drug treatment as shown in Table 3.

In the PC-3 model, there was no beneficial effect of the combination as compared to single drug treatment. However, the optimal dose for single dose administration was not determined.

TABLE 2

DOSE RESPONSE OF COMPOUND (xvii) WITH AND WITHOUT PACLITAXEL AGAINST THE LX-1 IN VIVO TUMOR MODEL. LX-1#16									
DRUGS									
Compound (xvii)	Pacli- taxel	% Toxic	MTW d27	Net Log Cell	Total #	REGRESSIONS			
(IV)	(IV)	Death	% T/C	Kill	Animals	PARTIAL	COMPLETE	CURE	
Dose (mg/kg)									
0	10	0	10.5	-0.374	6	2			
25	0	0	3.94	-0.042	6				
15	0	0	12.24	-0.465	6				
7.5	0	0	19.06	-0.581	6				
25	10	0	1.28	0.382	6	4			
15	10	17	1.92	0.589	6	1			
7.5	10		4.57	-0.033	6				

\*Q2Dx3; 5,12,19 Paclitaxel injected one hour after Compound (xvii).

TABLE 3

DOSE RESPONSE OF COMPOUND (xvii) WITH AND WITHOUT PACLITAXEL AGAINST THE CX-1 IN VIVO TUMOR MODEL. CX-1#9									
DRUGS									
Compound (xvii)	Pacli- taxel	% Toxic	MTW d55	Net Log Cell	Total #	REGRESSIONS			
(IV)	(IV)	Death	% T/C	Kill	Animals	PARTIAL	COMPLETE	CURE	
Dose (mg/kg)									
0	10		38.12	-0.124	6	2			
25	0	83			6				
15	0		52.87	-0.313	6				
7.5	0		109.7	-0.763	6				
25	10		47.64	-0.354	6	2			
15	10		51.61	-0.39	6	2			
7.5	10		73.85	-0.531	6	1			

\*Q2Dx3; 5,12,19 Paclitaxel injected one hour after Compound (xvii).

TABLE 4

DOSE RESPONSE OF COMPOUND (xvii) WITH AND WITHOUT PACLITAXEL AGAINST THE PC-3 IN VIVO TUMOR MODEL. PC-3#8									
DRUGS									
Compound (xvii)	Pacli- taxel	% Toxic	MTW d35	Net Log Cell	Total #	REGRESSIONS			
(IV)	(IP)	Death	% T/C	Kill	Animals	PARTIAL	COMPLETE	CURE	
Dose (mg/kg)									
0	30	17	2	toxic	6	5			
0	20	0	2.86	1.98	6	5	1		
0	10	0	55.12	-0.672	6	2			
30	0	33	0.09	0.967	6	3	1		
30	30	33	0.09	0.603	6	4			
30	20	0	0.09	1.07	6	4			2
30	10	17	0.09	1.98	6	3			

\*Q2Dx3; 5,12,19 Paclitaxel injected one hour after Compound (xvii).

The following compounds were prepared and can be prepared according to the Examples:

3. Xaa Val Xab Pro Xac
4. Xaa Val Xab Pro Xad
5. Xaa Val Xab Pro Xae
6. Xaa Val Xab Pro Xaf

7. Xaa Val Xab Pro Xag  
 8. Xaa Val Xab Pro Xah  
 9. Xaa Val Xab Pro Xai  
 10. Xaa Val Xab Pro Xak  
 11. Xaa Val Xab Pro Xal  
 12. Xaa Val Xab Pro Xam  
 13. Xaa Val Xab Pro Xan  
 14. Xaa Val Xab Pro Xao  
 15. Xaa Val Xab Pro Xap  
 16. Xaa Val Xab Pro Xaq  
 17. Xaa Val Xab Pro Xar  
 18. Xaa Val Xab Pro Xas  
 19. Xaa Val Xab Pro Xat  
 20. Xaa Val Xab Pro Xau  
 21. Xaa Val Xab Pro Xav  
 22. Xaa Val Xab Pro Xaw  
 23. Xaa Val Xab Pro Xax  
 24. Xaa Val Xab Pro Xay  
 25. Xaa Val Xab Pro Xaz  
 26. Xaa Val Xab Pro Xba  
 27. Xaa Val Xab Pro Xbb  
 28. Xaa Val Xbc Pro Xay  
 29. Xaa Val Xab Pro Xbd  
 30. Xaa Val Xab Pro Xbe  
 31. Xaa Val Xab Pro Xbf  
 32. Xaa Val Xab Pro Xbg  
 33. Xaa Val Xab Pro Xbh  
 34. Xaa Val Xab Pro Xbi  
 35. Xaa Val Xab Pro Xbk  
 36. Xaa Val Xab Pro Xbl  
 37. Xaa Val Xab Pro Xbm  
 38. Xaa Val Xab Pro Xbn  
 39. Xaa Val Xab Pro Xbo  
 40. Xaa Val Xab Pro Xbp  
 41. Xaa Val Xab Pro Xbq  
 42. Xaa Val Xab Pro Xbr  
 43. Xaa Val Xab Pro Xbs  
 44. Xaa Val Xab Pro Xbt  
 45. Xaa Val Xab Pro Xbu  
 46. Xaa Val Xab Pro Xbv  
 47. Xaa Val Xab Pro Xbw  
 48. Xaa Val Xab Pro Xbx  
 49. Xaa Val Xab Pro Xby  
 50. Xaa Val Xab Pro Xbz  
 51. Xaa Val Xab Pro Xca  
 52. Xaa Val Xab Pro Xcb  
 53. Xaa Val Xab Pro Xcc  
 54. Xaa Val Xab Pro Xcd  
 55. Xaa Val Xab Pro Xce  
 56. Xaa Val Xab Pro Xcf  
 57. Xaa Xdf Xab Pro Xay  
 58. Xaa Val Xab Pro Xch  
 59. Xaa Val Xab Pro Xci  
 60. Xaa Val Xab Pro Xck  
 61. Xaa Val Xab Pro Xcf  
 62. Xaa Val Xab Pro Xcm  
 63. Xaa Val Xab Pro Xcn  
 64. Xaa Val Xab Pro Xco  
 65. Xaa Val Xab Pro Xcp  
 66. Xaa Val Xab Pro Xcq  
 67. Xaa Val Xab Pro Xcr  
 68. Xaa Val Xab Pro Xcs  
 69. Xaa Val Xab Pro Xct  
 70. Xaa Val Xab Pro Xcu  
 71. Xcw Val Xab Pro Xcv  
 72. Xcx Val Xab Pro Xcv  
 73. Xaa Val Xab Pro Pro Xcy

74. Xaa Val Xab Pro Pro Xcz  
 75. Xaa Val Xda Pro Xcv  
 76. Xaa Xdb Xab Pro Xcv  
 77. Xdc Val Xab Pro Xcv  
 5 78. Xaa Ile Xab Pro Xcv  
 79. Xdd Val Xab Pro Xcv  
 80. Xde Val Xab Pro Xcv  
 81. Xaa Xdf Xab Pro Xcv  
 82. Xaa Val Xab Pro Xcg  
 10 83. Xaa Val Xab Pro Pro Xdg  
 84. Xaa Val Xab Pro Pro Xdh  
 85. Xaa Val Xab Pro Pro Xdi  
 86. Xaa Val Xab Pro Pro Xdk  
 87. Xaa Val Xdl Pro Xcv  
 15 88. Xde Val Xab Pro Xay  
 89. Xaa Val Xdl Pro Xay  
 90. Xaa Val Xab Pro Xdm  
 91. Xaa Val Xab Pro Xdn  
 92. Xaa Val Xab Pro Xdo  
 20 93. Xaa Val Xab Pro Xdp  
 94. Xaa Val Xab Pro Xdq  
 95. Xaa Val Xab Pro Pro Xdr  
 96. Xaa Val Xab Pro Xdq  
 97. Xaa Val Xbc Pro Xcv  
 25 98. Xaa Ile Xab Pro Xay  
 99. Xcw Val Xab Pro Xay  
 100. Xaa Val Xbc Pro Xal  
 101. Xaa Val Xdl Pro Xal  
 102. Xaa Xdf Xab Pro Xal  
 30 103. Xaa Ile Xab Pro Xal  
 104. Xdd Val Xab Pro Xal  
 105. Xde Val Xab Pro Xal  
 106. Xcx Val Xab Pro Xcy  
 107. Xcw Val Xab Pro Xal  
 35 108. Xcx Val Xab Pro Xal  
 109. Xcw Val Xab Pro Xav  
 110. Xcx Val Xab Pro Xav  
 111. Xcw Val Xab Pro Xaw  
 112. Xcx Val Xab Pro Xaw  
 40 113. Xab Val Xab Pro Xay  
 114. Xab Val Xab Pro Xcv  
 115. Xab Val Xab Pro Xal  
 116. Xab Val Xab Pro Xam  
 117. Xab Val Xab Pro Xan  
 45 118. Xab Val Xab Pro Xao  
 119. Xab Val Xab Pro Xav  
 120. Xab Val Xab Pro Xaw  
 121. Xab Val Xab Pro Xat  
 122. Xab Val Xab Pro Xau  
 50 123. Xab Val Xab Pro Xbf  
 124. Xab Val Xab Pro Xbm  
 125. Xab Val Xab Pro Xbn  
 126. Xab Val Xab Pro Xbo  
 127. Xab Val Xab Pro Xch  
 55 128. Xaa Val Xab Pro Xdt  
 129. Xaa Val Xab Pro Xdu  
 130. Xaa Val Xab Pro Xdv  
 131. Xaa Val Xab Pro Xdw  
 132. Xaa Val Xab Pro Xdx  
 60 133. Xaa Val Xab Pro Xdy  
 134. Xaa Val Xab Pro Xdz  
 135. Xaa Val Xab Pro Xea  
 136. Xaa Val Xab Pro Xeb  
 137. Xaa Val Xab Pro Xec  
 65 138. Xaa Val Xab Pro Xed  
 139. Xaa Val Xab Pro Xef  
 140. Xaa Val Xab Pro Xeg

- 141. Xaa Val Xab Pro Xeh
- 142. Xaa Val Xab Pro Xei
- 143. Xaa Val Xab Pro Xek
- 144. Xaa Val Xab Pro Xel
- 145. Xaa Val Xab Pro Xem
- 146. Xaa Val Xab Pro Xen
- 147. Xaa Val Xab Pro Xeo
- 148. Xaa Val Xab Pro Xep
- 149. Xaa Val Xab Pro Xeq
- 150. Xaa Val Xab Pro Xer
- 151. Xaa Val Xab Pro Xcq
- 152. Xaa Val Xab Pro Pro Val Phe
- 153. Xaa Val Xab Pro Xet Val Phe NH<sub>2</sub>
- 154. Xaa Val Xer Pro Pro Val Phe NH<sub>2</sub>
- 155. Xaa Val Xbc Pro Pro Val Phe NH<sub>2</sub>
- 156. Xaa Ile Xab Pro Pro Val Phe NH<sub>2</sub>
- 157. Xaa Leu Xab Pro Pro Val Phe NH<sub>2</sub>
- 158. Xde Val Xab Pro Pro Val Phe NH<sub>2</sub>
- 159. Xdd Val Xab Pro Pro Val Phe NH<sub>2</sub>
- 160. Xes Val Xab Pro Pro Val Phe NH<sub>2</sub>
- 161. Xeu Val Xab Pro Pro Val Phe NH<sub>2</sub>
- 162. Xaa Val Xab Pro Pro Phe Phe NH<sub>2</sub>
- 163. Xaa Val Xab Pro Pro Val NH<sub>2</sub>
- 164. Xaa Val Xab Pro Xev
- 165. Xaa Val Xab Pro Pro NH<sub>2</sub>
- 166. Xaa Val Xab Pro Pro
- 167. Xaa Val Xab Pro Xew
- 168. Xaa Val Xab Xex
- 169. Xdd Val Xab Pro Pro NH<sub>2</sub>
- 170. Xaa Xdf Xab Pro Pro NH<sub>2</sub>
- 171. Xaa Val Xab Pro Xey
- 172. Xaa Val Xab Pro Xez
- 173. Xfa Val Xab Pro Pro Val Phe NH<sub>2</sub>
- 174. Xaa Val Xab Pro Pro Xfb
- 175. Xaa Val Xab Pro Xfc
- 176. Xaa Val Xab Pro Xfd
- 177. Xaa Val Xab Pro Xfe
- 178. Xaa Val Xab Pro Xff
- 179. Xaa Val Xab Pro Xfg
- 180. Xaa Val Xab Pro Xfh
- 181. Xaa Val Xab Pro Xfi
- 182. Xaa Val Xab Pro Xfj
- 183. Xaa Val Xdl Pro Pro NH<sub>2</sub>
- 184. Xaa Val Xfk Pro Pro NH<sub>2</sub>
- 185. Xaa Val Xfl Pro Xfh
- 186. Xaa Val Xfk Pro Xfh
- 187. Xcx Val Xab Pro Xfh
- 188. Xaa Val Xab Pro Pro Xdf Phe NH<sub>2</sub>
- 189. Xaa Val Xab Pro Pro Leu Phe NH<sub>2</sub>
- 190. Xaa Val Xab Pro Pro le Phe NH<sub>2</sub>

TABLE 5

SEQUENCE IDENTIFICATION OF COMPOUNDS PREPARED ACCORDING TO THE EXAMPLES AND CONTAINED IN FIGS. 1A-1D	
Compound Number(s)	SEQ ID NO:
2A, 3-56, 58-72, 75, 77, 79-80, 82, 87-94, 96-97, 99-101, 104-151, 164, 167, 171-172, 175-182, 185-187, and Compounds i-xvii of the FIGS. 1A-1D	1
57	2
73-74, 83-86, 95, 174	3
76, 81, 102	4
78, 98, 103	5
1A, 152, 154-155, 158-161, 173	6

TABLE 5-continued

SEQUENCE IDENTIFICATION OF COMPOUNDS PREPARED ACCORDING TO THE EXAMPLES AND CONTAINED IN FIGS. 1A-1D	
Compound Number(s)	SEQ ID NO:
153	7
156	8
157	9
162	10
163	11
1B, 2B, 165-166, 169, 183	12
168	13
170	14
188	15
189	16
190	17

Examples for the MS-characterization of the synthesized novel compounds are listed below:

EXAMPLE

Fast Atom Bombardment MS Analysis

EXAMPLE	Fast atom bombardment MS analysis
3.	565
4.	579
5.	593
6.	607
7.	621
8.	635
11.	607
12.	607
13.	621
14.	649
15.	635
16.	635
17.	635
18.	635
19.	621
20.	621
21.	635
22.	635
25.	633
26.	647
27.	661
31.	623
32.	671
33.	667
34.	681
35.	655
36.	655
37.	669
38.	621
39.	635
41.	649
42.	621
43.	633
44.	667
45.	607
46.	647
47.	668
48.	655
49.	669
50.	685
51.	629
52.	625
53.	721
55.	579
58.	623
61.	597
62.	621

-continued

EXAMPLE	Fast atom bombardment MS analysis
63.	609
64.	625
65.	635
66.	591
67.	715
68.	685
69.	685
70.	591
71.	607
72.	621
74.	706
75.	579
76.	579
77.	579
78.	607
79.	607
80.	607
81.	607
82.	637
83.	692
84.	706
85.	706
86.	706
87.	607
90.	635
92.	659
93.	617
94.	636
95.	678
128.	671
131.	625
139.	625
151.	637
152.	798
153.	810
154.	812
155.	812
156.	812
157.	812
258.	812
159.	811
160.	825
161.	881
162.	845
163.	649
164.	737
165.	550
166.	551
167.	731
168.	550
169.	566
170.	566
171.	635
172.	704
173.	853
174.	740
175.	619
176.	845
177.	649
178.	691
179.	717
180.	641
181.	579
182.	595
183.	566
184.	566
185.	669
186.	656
187.	669
188.	811
189.	812
190.	812

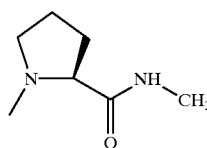
The symbols used in the description of the compounds of Formula I have the following meanings:

5 Xaa: N,N-Dimethylvaline

Xab: N-Methylvaline

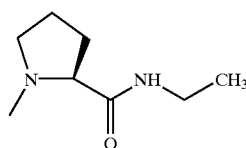
Xac:

10



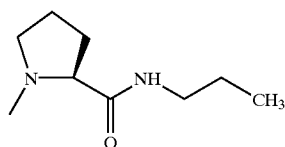
Xad:

15



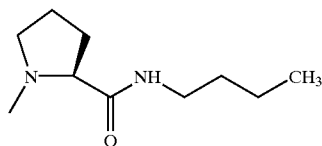
Xae:

20



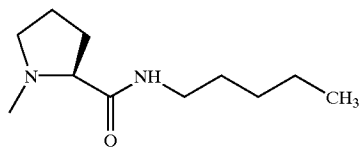
Xaf:

25



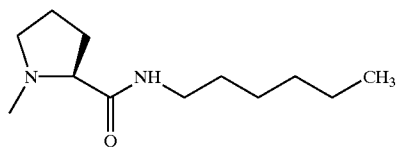
Xag:

30



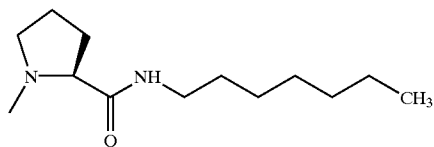
Xah:

35



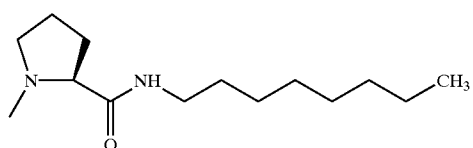
Xai:

40



Xak:

45



50

55

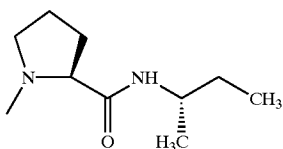
60

65

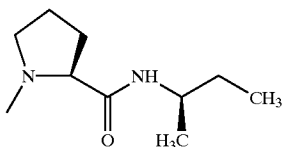
37

-continued

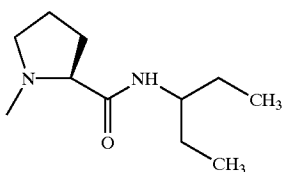
Xal:



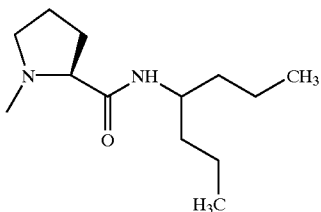
Xam:



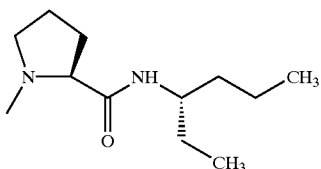
Xan:



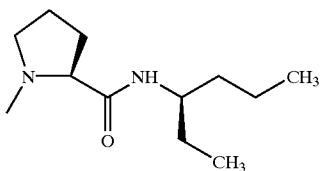
Xao:



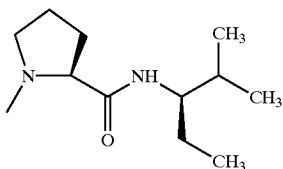
Xap:



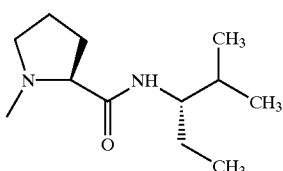
Xaq:



Xar:



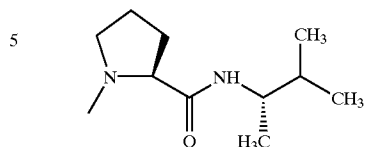
Xas:



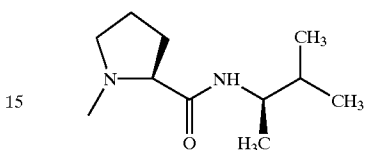
38

-continued

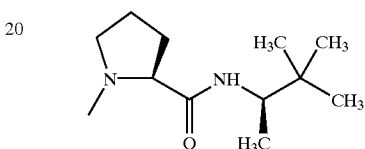
Xat:



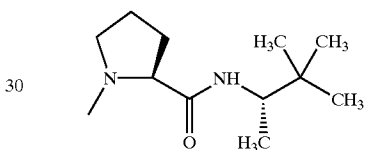
10 Xau:



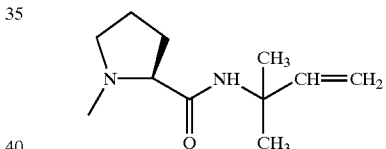
Xav:



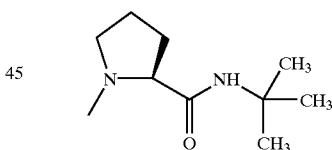
25 Xaw:



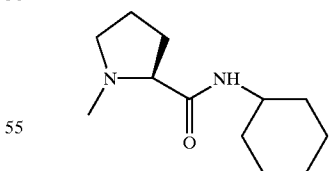
Xax:



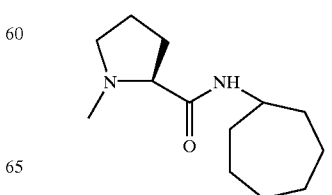
40 Xay:



Xaz:



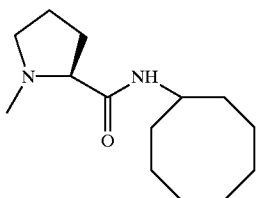
60 Xba:



39

-continued

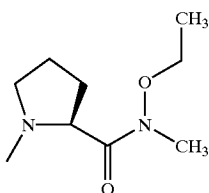
Xbb:



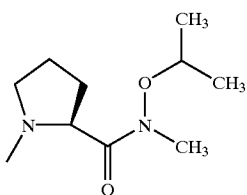
Xbc:

N-Methyl-isoleucine

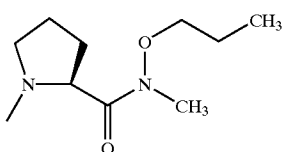
Xbd:



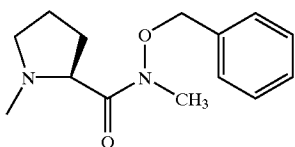
Xbe:



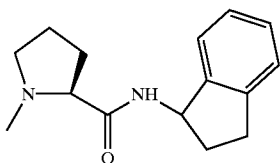
Xbf:



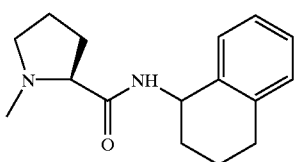
Xbg:



Xbh:



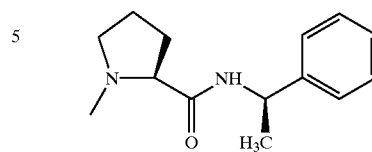
Xbi:



40

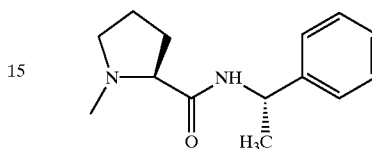
-continued

Xbk:

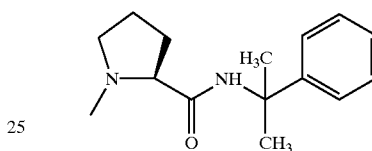


10

Xbl:

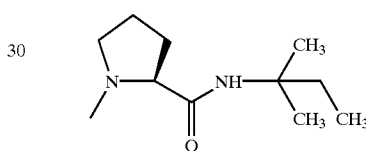


Xbm:



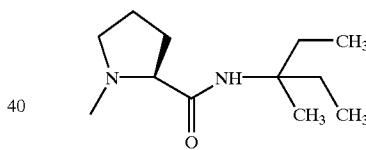
25

Xbn:

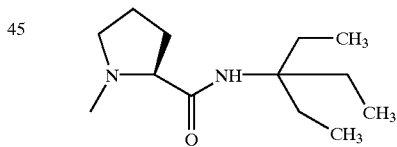


35

Xbo:

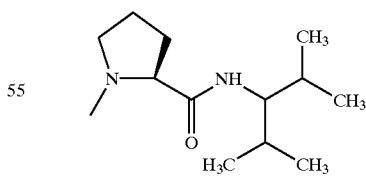


Xbp:



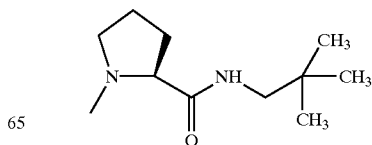
50

Xbq:



60

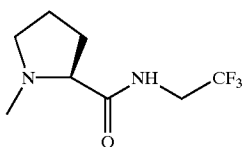
Xbr:



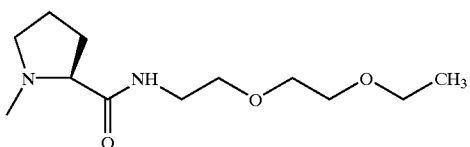
41

-continued

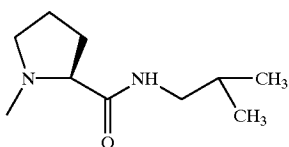
Xbs:



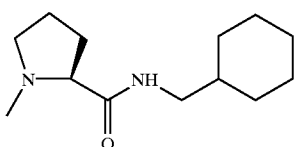
Xbt:



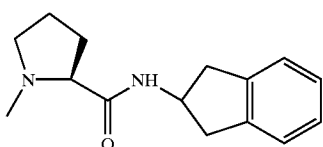
Xbu:



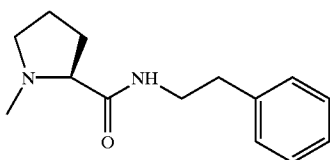
Xbv:



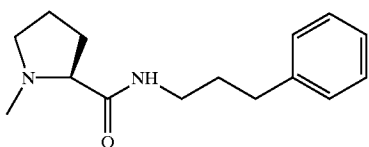
Xbw:



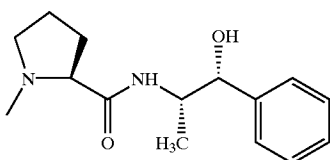
Xbx:



Xby:



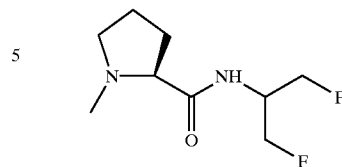
Xbz:



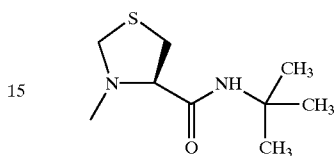
42

-continued

Xca:



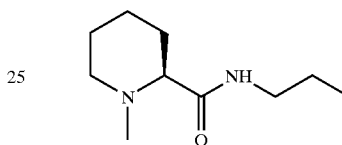
10 Xcb:



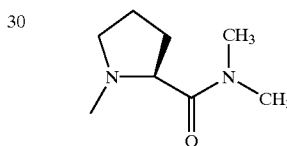
Xcc:

20 Proline adamantyl (1) amide

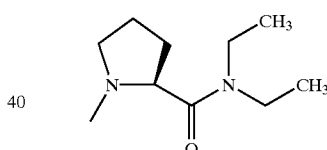
Xcd:



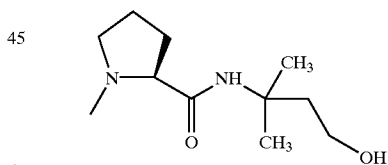
Xce:



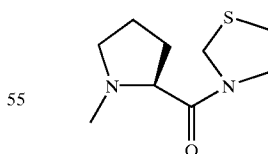
35 Xcf:



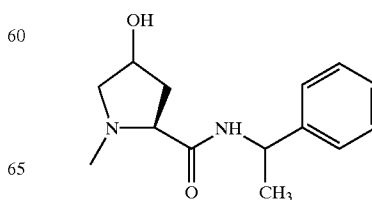
Xcg:



50 Xch:



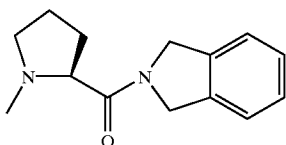
Xci:



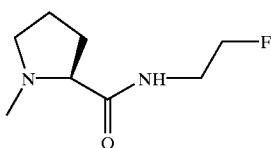
**43**

-continued

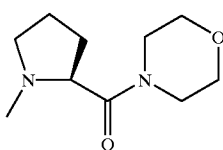
Xck:



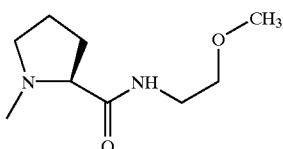
Xcl:



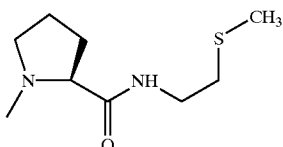
Xcm:



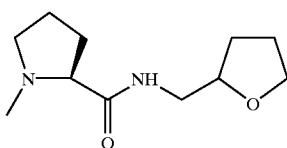
Xcn:



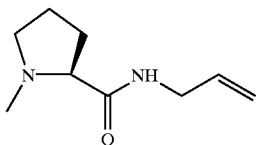
Xco:



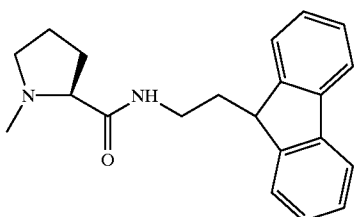
Xcp:



Xcq:



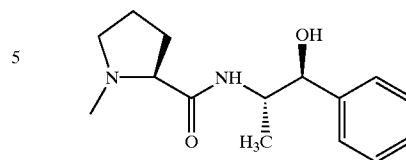
Xcr:



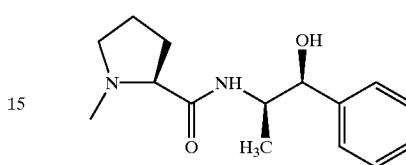
**44**

-continued

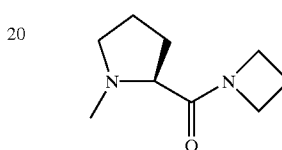
Xcs:



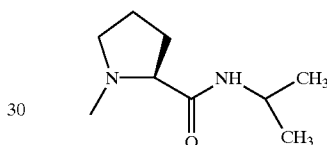
10 Xct:



Xcu:



25 Xcv:



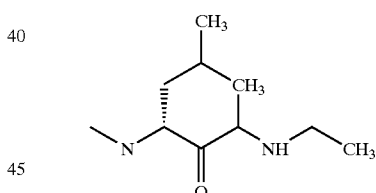
Xcw:

N-Methyl-N-ethyl-valine

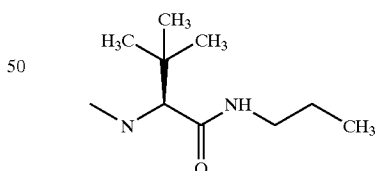
35 Xcx:

N, N-Diethylvaline

Xcy:



Xcz:



55 Xda:

N-Methyl-2-aminobutyryl

Xdb:

2-aminobutyryl

60 Xdc:

N, N-Dimethyl-2-aminobutyryl

Xdd:

65 N, N-Dimethyl-2-tert. butylglycine

45

-continued

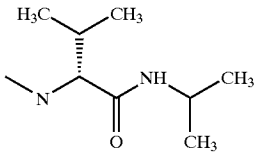
Xde:

N, N-Dimethyl-isoleucine

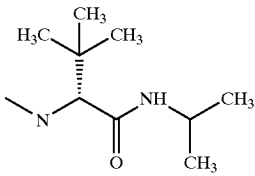
Xdf:

2-tert. butylglycine

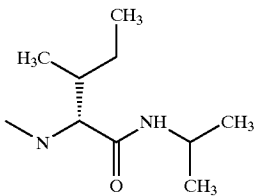
Xdg:



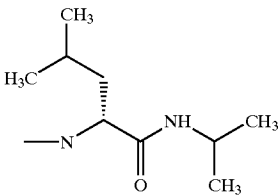
Xdh:



Xdi:



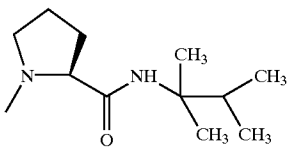
Xdk:



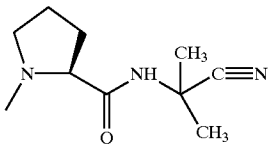
Xdl:

N-Methyl-2-tert. butylglycine

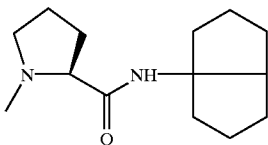
Xdm:



Xdn:



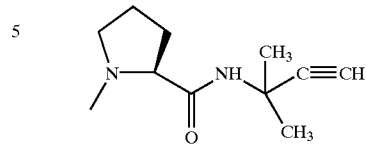
Xdo:



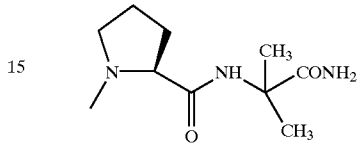
46

-continued

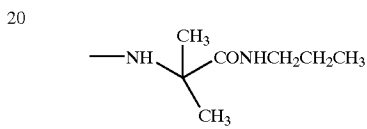
Xdp:



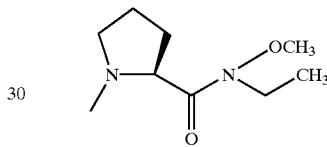
Xdq:



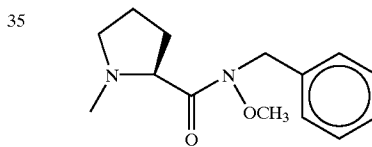
Xdr:



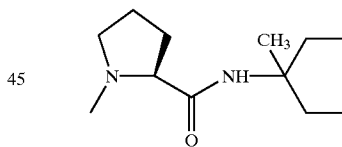
Xds:



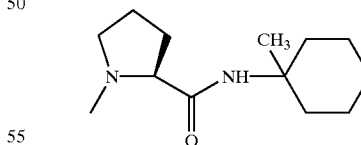
Xdt:



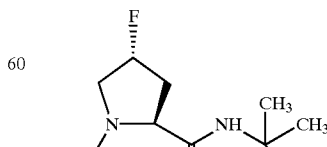
Xdu:



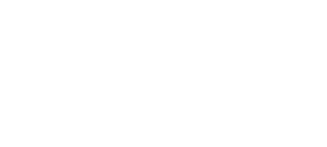
Xdv:



Xdw:



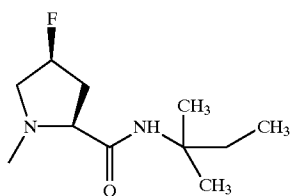
45



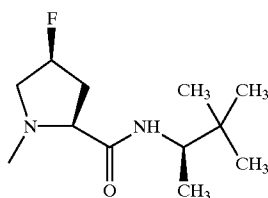
47

-continued

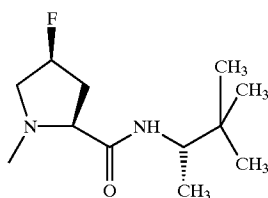
Xdx:



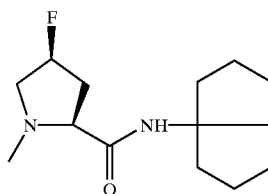
Xdy:



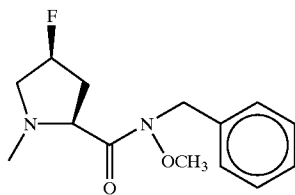
Xdz:



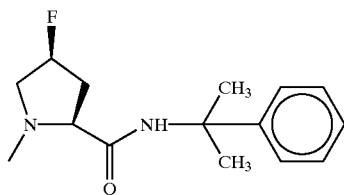
Xea:



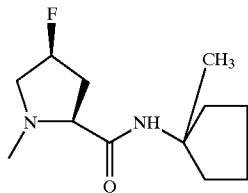
Xeb:



Xec:



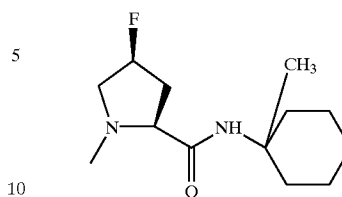
Xed:



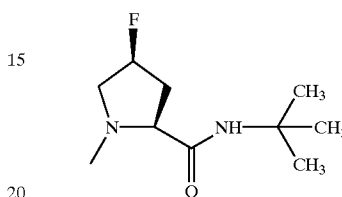
48

-continued

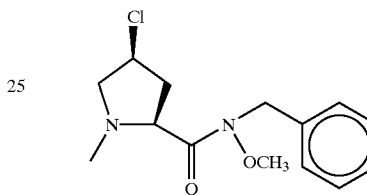
Xee:



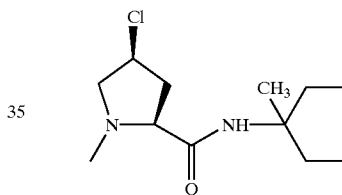
Xef:



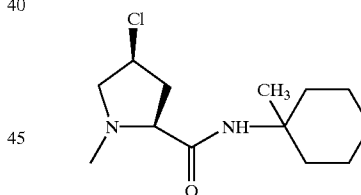
Xeg:



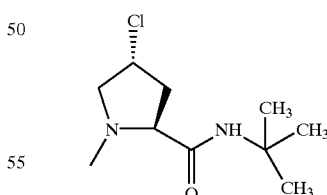
Xeh:



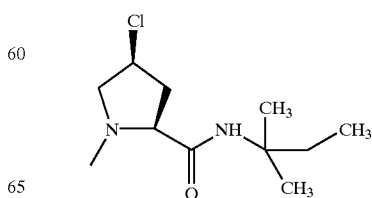
Xei:



Xek:



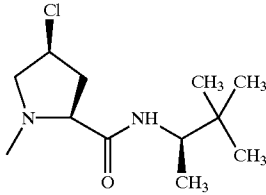
Xel:



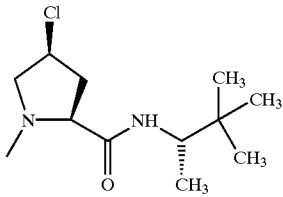
49

-continued

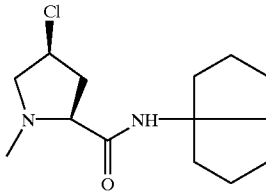
Xem:



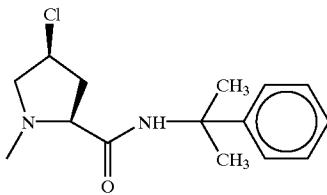
Xen:



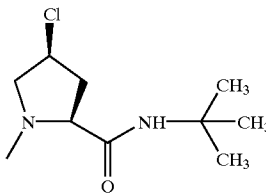
Xeo:



Xep:



Xeq:



Xer:

N-Methylleucine

Xes:

N-Acetyl-N-methylvaline

Xet:

pipecolic acid

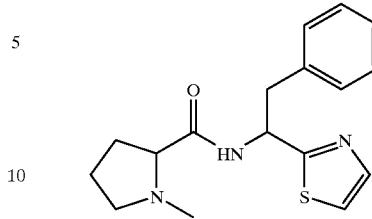
Xeu:

N, N-Dibutylvaline

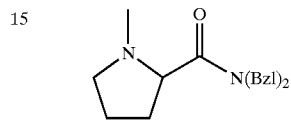
50

-continued

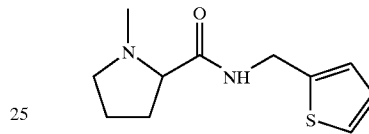
Xev:



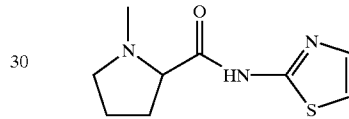
Xew:



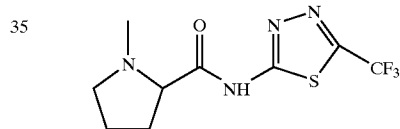
Xex:



Xey:



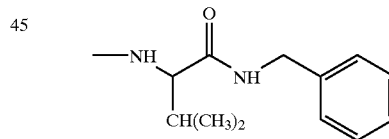
Xez:



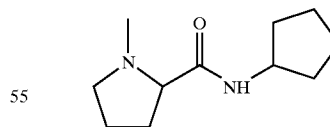
Xfa:

N, N-dipropylvaline

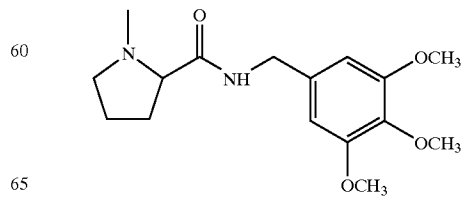
Xfb:



Xfc:



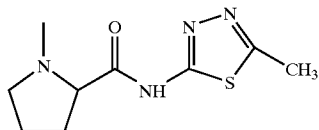
Xfd:



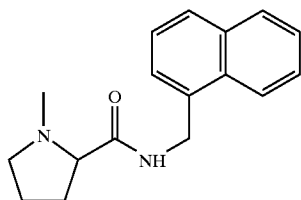
51

-continued

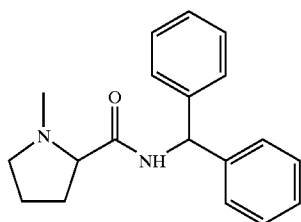
Xfe:



Xff:



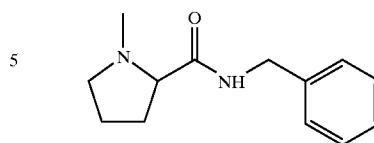
Xfg:



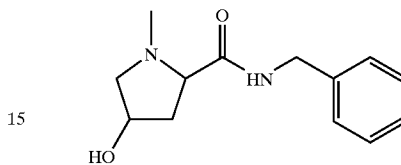
52

-continued

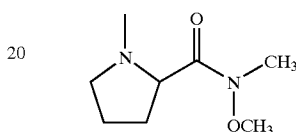
Xfh:



10 Xfi:



Xfj:



25 Xfk: N-Ethylvaline

Xfl: N-Methyl-3-tert-butylalanine

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(iii) NUMBER OF SEQUENCES: 17

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: <Unknown>
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Xaa Val Xaa Pro Xaa  
1 5

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: <Unknown>
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Xaa Xaa Xaa Pro Xaa  
1 5

-continued

## (2) INFORMATION FOR SEQ ID NO: 3:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 6 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: <Unknown>
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Xaa Val Xaa Pro Pro Xaa  
 1                   5

## (2) INFORMATION FOR SEQ ID NO: 4:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 5 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: <Unknown>
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Xaa Xaa Xaa Pro Xaa  
 1                   5

## (2) INFORMATION FOR SEQ ID NO: 5:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 5 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: <Unknown>
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Xaa Ile Xaa Pro Xaa  
 1                   5

## (2) INFORMATION FOR SEQ ID NO: 6:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 7 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: <Unknown>
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Xaa Val Xaa Pro Pro Val Phe  
 1                   5

## (2) INFORMATION FOR SEQ ID NO: 7:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 7 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: <Unknown>
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Xaa Val Xaa Pro Xaa Val Phe

-continued

1 5

## (2) INFORMATION FOR SEQ ID NO: 8:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 7 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: <Unknown>
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Xaa Ile Xaa Pro Pro Val Phe  
1 5

## (2) INFORMATION FOR SEQ ID NO: 9:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 7 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: <Unknown>
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Xaa Leu Xaa Pro Pro Val Phe  
1 5

## (2) INFORMATION FOR SEQ ID NO: 10:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 7 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: <Unknown>
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Xaa Val Xaa Pro Pro Phe Phe  
1 5

## (2) INFORMATION FOR SEQ ID NO: 11:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 6 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: <Unknown>
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Xaa Val Xaa Pro Pro Val  
1 5

## (2) INFORMATION FOR SEQ ID NO: 12:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 5 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: <Unknown>
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

-continued

Xaa Val Xaa Pro Pro  
1 5

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 4 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: <Unknown>  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Xaa Val Xaa Xaa  
1

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 5 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: <Unknown>  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Xaa Xaa Xaa Pro Pro  
1 5

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 7 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: <Unknown>  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Xaa Val Xaa Pro Pro Xaa Phe  
1 5

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 7 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: <Unknown>  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Xaa Val Xaa Pro Pro Leu Phe  
1 5

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 7 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: <Unknown>  
(D) TOPOLOGY: linear

-continued

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

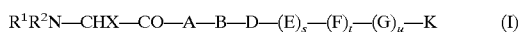
Xaa Val Xaa Pro Pro Ile Phe  
1 5

What is claimed is:

1. A pharmaceutical composition comprising:

an effective amount of a first compound selected from the group consisting of paclitaxel, taxotere, modified taxane and taxoid analogs; and

an enhanced effective amount of a second compound, wherein the second compound is of Formula I



wherein:

R<sup>1</sup> is alkyl, cycloalkyl, alkylsulfonyl, fluoroalkyl, or aminosulfonyl;

R<sup>2</sup> is hydrogen, alkyl, fluoroalkyl or cycloalkyl;

R<sup>1</sup>-N-R<sup>2</sup> together may be a pyrrolidino or piperidino residue;

A is a valyl, isoleucyl, leucyl, alloisoleucyl, 2,2-dimethylglycyl, 2-cyclopropylglycyl, 2-cyclopentylglycyl, 3-tert-butylalanyl, 2-tert-butylglycyl, 3-cyclohexylalanyl, 2-ethylglycyl, 2-cyclohexylglycyl, norleucyl or norvalyl residue;

B is a N-alkyl-valyl, -norvalyl, -leucyl, -isoleucyl, -2-tert-butylglycyl, -3-tert-butylalanyl, -2-ethylglycyl, -2-cyclopropylglycyl, -2-cyclopentylglycyl, -norleucyl or -2-cyclohexylglycyl residue;

D is a prolyl, homoprolyl, hydroxyprolyl, 3,4-dehydroprolyl, 4-fluoroprolyl, 3-methylprolyl, 4-methylprolyl, 5-methylprolyl, azetidine-2-carbonyl, 3,3-dimethylprolyl, 4,4-difluoroprolyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;

E is a prolyl, homoprolyl, hydroxyprolyl, 3,4-dehydroprolyl, 4-fluoroprolyl, 3-methylprolyl, 4-methyl prolyl, 5-methylprolyl, azetidine-2-carbonyl, 3,3-dimethylprolyl, 4,4-difluoroprolyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;

F and G are independently selected from the group consisting of prolyl, homoprolyl, hydroxyprolyl, thiazolidinyl-4-carbonyl, 1-aminopentyl-1-carbonyl, valyl, 2-tert-butylglycyl, isoleucyl, leucyl, 3-cyclohexylalanyl, phenylalanyl, N-methylphenylalanyl, tetrahydroisioquinolyl-2-histidyl, 1-aminoindyl-1-carbonyl, 3-pyridylalanyl, 2-cyclohexylglycyl, norleucyl, norvalyl, neopentylglycyl, tryptophanyl, glycyl, 2,2-dimethylglycyl, alanyl, β-alanyl and 3-naphthylalanyl residues;

X is hydrogen, alkyl, cycloalkyl, —CH<sub>2</sub>-cyclohexyl or arylalkyl;

s, t and u are independently 0 or 1; and

K is hydroxy, alkoxy, phenoxy, benzyloxy or an amino moiety of the formula R<sup>5</sup>-N-R<sup>6</sup> wherein:

R<sup>5</sup> is hydrogen; hydroxy; C<sub>1-7</sub> alkoxy; benzyloxy; phenyloxy; fluorine substituted or unsubstituted C<sub>1-7</sub>-linear or branched alkyl; C<sub>1-12</sub> linear or branched hydroxyalkyl; C<sub>3-10</sub>-cycloalkyl; unsubstituted benzyl; or

mono-, di- or tri-substituted benzyl, wherein the substituents are independently selected from the group consisting of: CF<sub>3</sub>, nitro, C<sub>1-7</sub> alkylsulfonyl, C<sub>1-4</sub> alkoxy, phenoxy, benzyloxy, halogen, C<sub>1-4</sub>-alkyl, cyano, hydroxy, N(CH<sub>3</sub>)<sub>2</sub>, COOMe, COOEt, COOiPr, and COONH<sub>2</sub>;

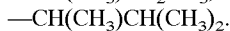
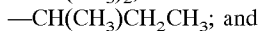
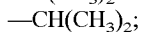
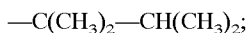
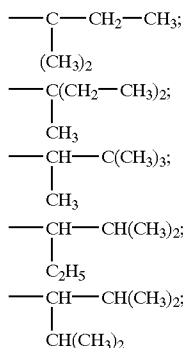
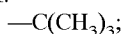
R<sup>6</sup> is hydrogen; fluorine substituted or unsubstituted C<sub>1-12</sub> linear or branched alkyl; C<sub>1-12</sub> linear or branched hydroxyalkyl; C<sub>3-10</sub>-cycloalkyl; —(CH<sub>2</sub>)<sub>v</sub>-C<sub>3-7</sub>-cycloalkyl (v=0,1,2, or 3); norephedryl; norpseudoephedryl; quinolyl; pyrazyl; —CH<sub>2</sub>-benzimidazolyl; (1)-adamantyl; (2)-adamantyl; —CH<sub>2</sub>-adamantyl; alpha-methyl-benzyl; alpha-dimethylbenzyl; —(CH<sub>2</sub>)<sub>v</sub>-phenyl (v=0,1,2, or 3) wherein the phenyl group is unsubstituted or mono- or di-substituted and the substituents are independently selected from the group consisting of: CF<sub>3</sub>, nitro, C<sub>1-7</sub> alkylsulfonyl, C<sub>1-4</sub> alkoxy, phenoxy, benzyloxy, halogen, C<sub>1-4</sub>-alkyl or fused alkyl, cyano, hydroxy, N(CH<sub>3</sub>)<sub>2</sub>, COOMe, COOEt, COOiPr, and COONH<sub>2</sub>; —(CH<sub>2</sub>)<sub>m</sub>-naphthyl (m=0 or 1); —(CH<sub>2</sub>)<sub>w</sub>-benzhydryl (w=0,1, or 2); biphenyl; picolyl; benzothiazolyl; benzisothiazolyl; benzopyrazolyl; benzoxazolyl; —(CH<sub>2</sub>)<sub>m</sub>-fluorenyl (m=0 or 1); pyrimidyl; —(CH<sub>2</sub>)<sub>m</sub>-indanyl (m=0 or 1); —(CH<sub>2</sub>CH<sub>2</sub>O)<sub>y</sub>-CH<sub>3</sub> (y=0,1,2,3,4, or 5); —(CH<sub>2</sub>CH<sub>2</sub>O)<sub>y</sub>-CH<sub>2</sub>CH<sub>3</sub> (y=0,1,2,3,4, or 5) NH-phenyl wherein the phenyl group is unsubstituted or mono- or di-substituted and the substituents are independently selected from the group consisting of: CF<sub>3</sub>, nitro, C<sub>1-7</sub> alkylsulfonyl, C<sub>1-4</sub> alkoxy, halogen, C<sub>1-4</sub> alkyl or fused alkyl, cyano, hydroxy, COOMe, COOEt, COOiPr, and COONH<sub>2</sub>; —NCH<sub>3</sub>-C<sub>6</sub>H<sub>5</sub>; —NH-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>; —NCH<sub>3</sub>-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>; 5-membered unsubstituted or mono- or di-substituted heteroaryl wherein the substituents are selected from the group consisting of: CF<sub>3</sub>, nitro, thiomethyl, thioethyl, C<sub>3-6</sub>-cycloalkyl, —CH<sub>2</sub>-COOEt, C<sub>3-4</sub>-alkylene group forming a bicyclic system with the heterocycle; phenyl; —CHR<sup>7</sup>-5-membered heteroaryl wherein the heteroaryl group is unsubstituted or mono- or di-substituted and the substituents are selected from the group consisting of: CF<sub>3</sub>, nitro, cyano, halogen, COOMe, COOEt, COOiPr, CONH<sub>2</sub>, C<sub>1-4</sub>-alkyl, C<sub>1-4</sub>-alkoxy, phenyl, benzyl, naphthyl, and C<sub>1-7</sub>-alkylsulfonyl; R<sup>7</sup> is hydrogen, linear or branched C<sub>1-5</sub> alkyl, and benzyl; or R<sup>7</sup> and R<sup>5</sup> together form a group —(CH<sub>2</sub>)<sub>3</sub>— or —(CH<sub>2</sub>)<sub>4</sub>—; and the salts thereof physiologically tolerated acids.

2. The pharmaceutical composition of claim 1 further comprising a pharmaceutically acceptable carrier.

3. A composition of claim 1 wherein for the compound of Formula I R<sup>1</sup> and R<sup>2</sup> are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, -2-ethylglycyl, -1-isoleucyl or -2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or

61

hydroxypropyl; and K is a substituted amino moiety having the formula  $R^5-N-R^6$  wherein  $R^5$  is hydrogen or  $C_1-C_4$  alkoxy and  $R^6$  is a  $C_{1-12}$  linear or branched alkyl group selected from the group of monovalent radicals consisting of:



4. A composition of claim 3 wherein the monovalent radical is  $-C(CH_3)_3$ .

5. A composition of claim 1 wherein for the compound of Formula I  $R^1$  and  $R^2$  are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, -2-ethylglycyl, -1-isoleucyl or -2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxypropyl; and K is a substituted amino moiety having the formula  $R^5-N-R^6$  wherein  $R^5$  is hydrogen or  $C_1-C_4$  alkoxy and  $R^6$  is selected from the group of monovalent radicals consisting of:  $(CH_2)_v$ -phenyl (wherein v is 1) and  $\alpha,\alpha$ -dimethylbenzyl.

6. A composition of claim 1 wherein for the compound of Formula I  $R^1$  and  $R^2$  are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, -2-ethylglycyl, -1-isoleucyl or -2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxypropyl; and K is a substituted amino moiety having the formula  $R^5-N-R^6$  wherein  $R^5$  is hydrogen or  $C_1-C_4$  alkoxy and  $R^6$  is a  $C_1-C_{12}$  linear or branched hydroxyalkyl.

7. A composition of claim 6 wherein  $R^6$  is 3-hydroxy-1, 1-dimethylpropyl.

8. A composition of claim 1 wherein for the compound of Formula I  $R^1$  and  $R^2$  are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, -2-ethylglycyl, -1-isoleucyl or -2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxypropyl; and K is a substituted amino moiety having the formula  $R^5-N-R^6$  wherein  $R^5$  is hydrogen or  $C_1-C_4$  alkoxy and  $R^6$  is a  $C_{3-10}$  cycloalkyl selected from the group consisting of: (1)-adamantyl, (2)-adamantyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl, 1-methylcyclohexyl and octa-1-yl.

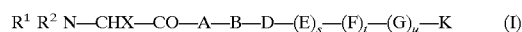
62

9. A composition of claim 1 wherein for the compound of Formula I  $R^1$  and  $R^2$  are each methyl; X is isopropyl; s is 1; t and u are each 0; A is valyl; B is N-methylvalyl; D is prolyl; E is prolyl;  $R^5$  is benzyl and  $R^6$  is hydrogen.

10. A method for treating cancer in a mammal, selected from the group consisting of: lung, breast, colon, prostate, bladder, rectal, endometrial and hematological cancers, comprising:

administering to said mammal an effective amount of a first compound selected from the group consisting of paclitaxel, taxotere, modified taxane and taxoid analogs; and

administering to said mammal an enhanced effective amount of a second compound of Formula I:



wherein:

$R^1$  is alkyl, cycloalkyl, alkylsulfonyl, fluoroalkyl, or aminosulfonyl;

$R^2$  is hydrogen, alkyl, fluoroalkyl or cycloalkyl;

$R^1-N-R^2$  together may be a pyrrolidino or piperidino residue;

A is a valyl, isoleucyl, leucyl, alloisoleucyl, 2,2-dimethylglycyl, 2-cyclopropylglycyl, 2-cyclopentylglycyl, 3-tert-butylalanyl, 2-tert-butylglycyl, 3-cyclohexylalanyl, 2-ethylglycyl, 2-cyclohexylglycyl, norleucyl or norvalyl residue;

B is a N-alkyl-valyl, -norvalyl, -leucyl, -isoleucyl, -2-tert-butylglycyl, -3-tert-butylalanyl, -2-ethylglycyl, -2-cyclopropylglycyl, -2-cyclopentylglycyl, -norleucyl or -2-cyclohexylglycyl residue;

D is a prolyl, homoprolyl, hydroxypropyl, 3,4-dehydroprolyl, 4-fluoroprolyl, 3-methylprolyl, 4-methylprolyl, 5-methylprolyl, azetidine-2-carbonyl, 3,3-dimethylprolyl, 4,4-difluoroprolyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;

E is a prolyl, homoprolyl, hydroxypropyl, 3,4-dehydroprolyl, 4-fluoroprolyl, 3-methylprolyl, 4-methyl prolyl, 5-methylprolyl, azetidine-2-carbonyl, 3,3-dimethylprolyl, 4,4-difluoroprolyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;

F and G are independently selected from the group consisting of prolyl, homoprolyl, hydroxypropyl, thiazolidinyl-4-carbonyl, 1-aminopentyl-1-carbonyl, valyl, 2-tert-butylglycyl, isoleucyl, leucyl, 3-cyclohexylalanyl, phenylalanyl, N-methylphenylalanyl, tetrahydroisoquinolyl-2-histidyl, 1-aminoindyl-1-carbonyl, 3-pyridylalanyl, 2-cyclohexylglycyl, norleucyl, norvalyl, neopentylglycyl, tryptophanyl, glycyl, 2,2-dimethylglycyl, alanyl,  $\beta$ -alanyl and 3-naphthylalanyl residues;

X is hydrogen, alkyl, cycloalkyl,  $-CH_2$ -cyclohexyl or arylalkyl;

s, t and u are independently 0 or 1; and

K is hydroxy, alkoxy, phenoxy, benzyloxy or an amino moiety of the formula  $R^5-N-R^6$  wherein:

$R^5$  is hydrogen; hydroxy;  $C_{1-7}$  alkoxy; benzyloxy; phenoxy; fluorine substituted or unsubstituted  $C_{1-7}$ -linear or branched alkyl;  $C_{1-12}$  linear or branched hydroxyalkyl;  $C_{3-10}$ -cycloalkyl; unsubstituted benzyl; or mono-, di- or tri-substituted benzyl, wherein the substituents are independently

selected from the group consisting of: CF<sub>3</sub>, nitro, C<sub>1-7</sub> alkylsulfonyl, C<sub>1-4</sub> alkoxy, phenoxy, benzoxy, halogen, C<sub>1-4</sub>-alkyl, cyano, hydroxy, N(CH<sub>3</sub>)<sub>2</sub>, COOMe, COOEt, COOiPr, and COONH<sub>2</sub>;

R<sup>6</sup> is hydrogen; fluorine substituted or unsubstituted C<sub>1-12</sub> linear or branched alkyl; C<sub>1-12</sub> linear or branched hydroxyalkyl; C<sub>3-10</sub>-cycloalkyl; —(CH<sub>2</sub>)<sub>v</sub>—C<sub>3-7</sub>-cycloalkyl (v=0,1,2, or 3); norephedryl; norpseudoephedryl; quinoly; pyrazyl; —CH<sub>2</sub>-benzimidazolyl; (1)-adamantyl; (2)-adamantyl; —CH<sub>2</sub>-adamantyl; alpha-methylbenzyl; alpha-dimethylbenzyl; —(CH<sub>2</sub>)<sub>v</sub>-phenyl (v=0,1,2, or 3) wherein the phenyl group is unsubstituted or mono- or di-substituted and the substituents are independently selected from the group consisting of: CF<sub>3</sub>, nitro, C<sub>1-7</sub> alkylsulfonyl, C<sub>1-4</sub> alkoxy, phenoxy, benzoxy, halogen, C<sub>1-4</sub>-alkyl or fused alkyl, cyano, hydroxy, N(CH<sub>3</sub>)<sub>2</sub>, COOMe, COOEt, COOiPr, and COONH<sub>2</sub>; —(CH<sub>2</sub>)<sub>m</sub>-naphthyl (m=0 or 1); —(CH<sub>2</sub>)<sub>w</sub>-benzhydryl (w=0, 1, or 2); biphenyl; picoly; benzothiazolyl benzisothiazolyl; benzopyrazolyl; benzoxazolyl; —(CH<sub>2</sub>)<sub>m</sub>-fluorenyl (m=0 or 1); pyrimidyl; —(CH<sub>2</sub>)<sub>m</sub>-indanyl (m=0 or 1); —(CH<sub>2</sub>CH<sub>2</sub>O)<sub>y</sub>—CH<sub>3</sub> (y=0,1,2,3,4, or 5); —(CH<sub>2</sub>CH<sub>2</sub>O)<sub>y</sub>—CH<sub>2</sub>CH<sub>3</sub> (y=0,1,2,3,4, or 5) NH-phenyl wherein the phenyl group is unsubstituted or mono- or di-substituted and the substituents are independently selected from the group consisting of: CF<sub>3</sub>, nitro, C<sub>1-7</sub> alkylsulfonyl, C<sub>1-4</sub> alkoxy, halogen, C<sub>1-4</sub> alkyl or fused alkyl, cyano, hydroxy, COOMe, COOEt, COOiPr, and COONH<sub>2</sub>; —NCH<sub>3</sub>—C<sub>6</sub>H<sub>5</sub>; —NH—CH<sub>2</sub>—C<sub>6</sub>H<sub>5</sub>; —CH<sub>3</sub>—CH<sub>2</sub>—C<sub>6</sub>H<sub>5</sub>; 5-membered unsubstituted or mono- or di-substituted heteroaryl wherein the substituents are selected from the group consisting of: CF<sub>3</sub>, nitro, thiomethyl, thioethyl, C<sub>3-6</sub>-cycloalkyl, —CH<sub>2</sub>—COOEt, C<sub>3-4</sub>-alkylene group forming a bicyclic system with the heterocycle; phenyl; —CHR<sup>7</sup>-5-membered heteroaryl wherein the heteroaryl group is unsubstituted or mono- or di-substituted and the substituents are selected from the group consisting of: CF<sub>3</sub>, nitro, cyano, halogen, COOMe, COOEt, COOiPr, CONH<sub>2</sub>, C<sub>1-4</sub>-alkyl, C<sub>1-4</sub>-alkoxy, phenyl, benzyl, naphthyl, and C<sub>1-7</sub>-alkylsulfonyl; R<sup>7</sup> is hydrogen, linear or branched C<sub>1-5</sub> alkyl, and benzyl; or

R<sup>7</sup> and R<sup>5</sup> together form a group —(CH<sub>2</sub>)<sub>3</sub>— or —(CH<sub>2</sub>)<sub>4</sub>—;

and the salts thereof with physiologically tolerated acids.

11. A method of claim 10 wherein the compound of Formula I is administered first followed by administration of the first compound.

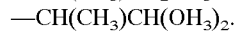
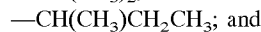
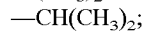
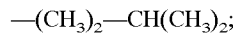
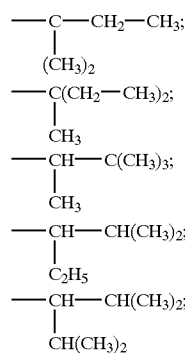
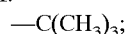
12. A method of claim 10 wherein the first compound is administered first followed by administration of the compound of Formula I.

13. A method of claim 10 wherein the first compound and the compound of Formula I are administered simultaneously.

14. A method of claim 10 wherein said mammal is human.

15. A method of claim 10 wherein for the compound of Formula I R<sup>1</sup> and R<sup>2</sup> are each methyl or ethyl; X is

isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, -2-ethylglycyl, -isoleucyl or -2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R<sup>5</sup>—N—R<sup>6</sup> wherein R<sup>5</sup> is hydrogen or C<sub>1</sub>—C<sub>4</sub> alkoxy and R<sup>6</sup> is a C<sub>1</sub>—C<sub>12</sub> linear or branched alkyl group selected from the group of monovalent radicals consisting of:



16. A method of claim 15 wherein said monovalent radical is —C(CH<sub>3</sub>)<sub>3</sub>.

17. A method of claim 10 wherein for the compound of Formula I R<sup>1</sup> and R<sup>2</sup> are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, -2-ethylglycyl, -1-isoleucyl or -2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R<sup>5</sup>—N—R<sup>6</sup> wherein R<sup>5</sup> is hydrogen or C<sub>1</sub>—C<sub>4</sub> alkoxy and R<sup>6</sup> is selected from the group of monovalent radicals consisting of: (CH<sub>2</sub>)<sub>v</sub>-phenyl (wherein v is 1), and α,α-dimethylbenzyl.

18. A method of claim 10 wherein for the compound of Formula I R<sup>1</sup> and R<sup>2</sup> are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, -2-ethylglycyl, -1-isoleucyl or -2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R<sup>5</sup>—N—R<sup>6</sup> wherein R<sup>5</sup> is hydrogen or C<sub>1</sub>—C<sub>4</sub> alkoxy and R<sup>6</sup> is a C<sub>1</sub>—C<sub>12</sub> linear or branched hydroxyalkyl.

19. A method of claim 18 wherein R<sup>6</sup> is 3-hydroxy-1,1-dimethylpropyl.

20. A method of claim 10 wherein for the compound of Formula I R<sup>1</sup> and R<sup>2</sup> are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, -2-ethylglycyl, -isoleucyl or

65

-2-tertbutylglycyl; D is prolyl, 4-fluoropropyl, thiazolidinyl-4-carbonyl, or 3,4-dehydropropyl; E is prolyl, 4-fluoropropyl, thiazolidinyl-4-carbonyl, homopropyl, 3,4-dehydropropyl or hydroxypropyl; and K is a substituted amino moiety having the formula  $R^5-N-R^6$  wherein  $R^5$  is hydrogen or  $C_1-C_4$  alkoxy and  $R^6$  is a  $C_{3-10}$  cycloalkyl selected from the group consisting of: (1)-adamantyl, (2)-adamantyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl, 1-methylcyclohexyl and octa-1-yl.

66

21. A method of claim 10 wherein for the compound of Formula I  $R^1$  and  $R^2$  are each methyl; X is isopropyl; s is 1; t and u are each 0; A is valyl; B is N-methylvalyl; D is prolyl; E is prolyl;  $R^5$  is benzyl and  $R^6$  is hydrogen.

22. The pharmaceutical composition of claim 1, wherein the first compound is selected from the group consisting of modified taxane and taxoid analogs.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 6,632,795 B1  
DATED : October 14, 2003  
INVENTOR(S) : Teresa Barlozzari et al.

Page 1 of 5

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Please replace drawing sheets, consisting of Figs. 1A-1D with the drawing sheets, consisting of Figs. 1A-1D, on the attached pages.

Column 59,

Line 28, after "leucyl", please delete "alloisoleucyl" and add -- allo-isoleucyl --.

Column 62,


Line 25, after "leucyl", please delete "alloisoleuscyl" and add -- allo-isoleucyl --.

Column 66,

Lines 5-7, please delete claim 22.

Signed and Sealed this

First Day of November, 2005

A handwritten signature in black ink on a light gray dotted background. The signature reads "Jon W. Dudas" in a cursive style.

JON W. DUDAS

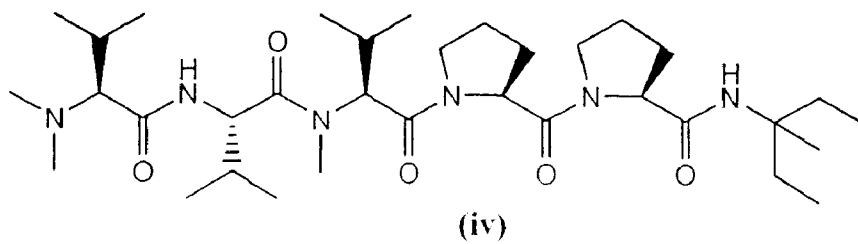
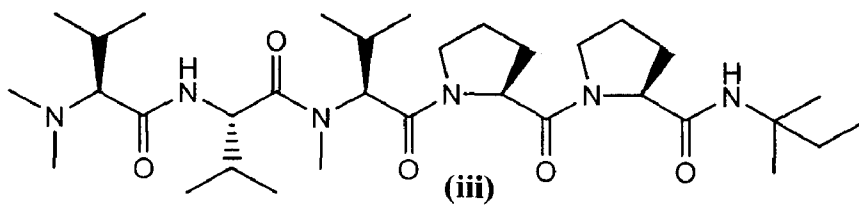
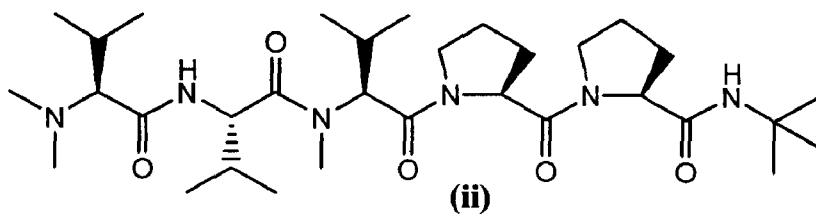
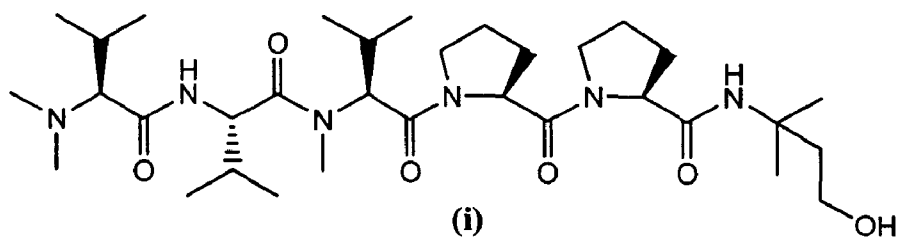
*Director of the United States Patent and Trademark Office*

U.S. Patent

Oct. 14, 2003

Sheet 1 of 4

6,632,795 B1

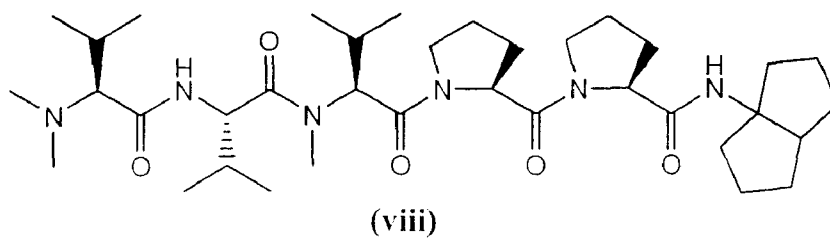
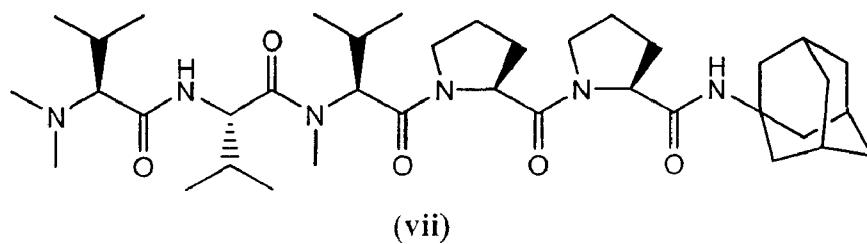
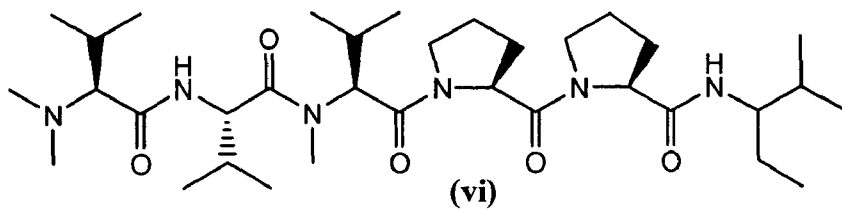
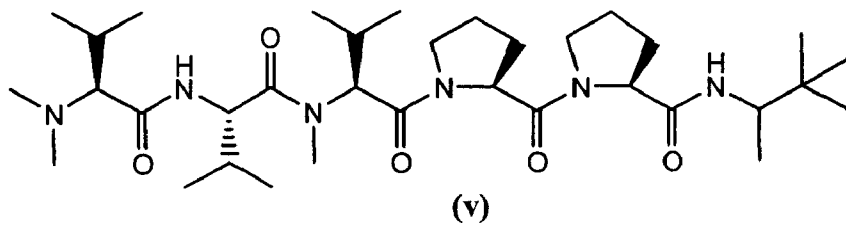


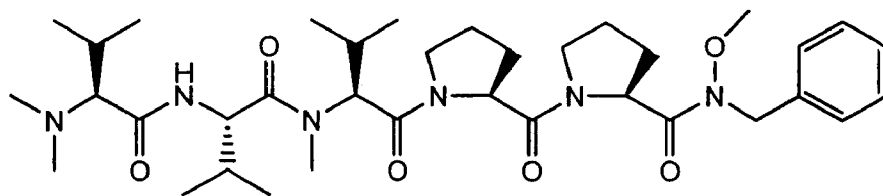
U.S. Patent

Oct. 14, 2003

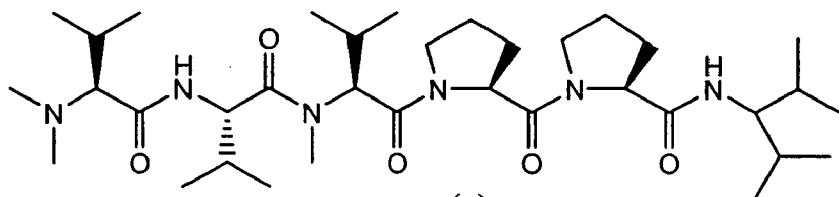
Sheet 2 of 4

6,632,795 B1

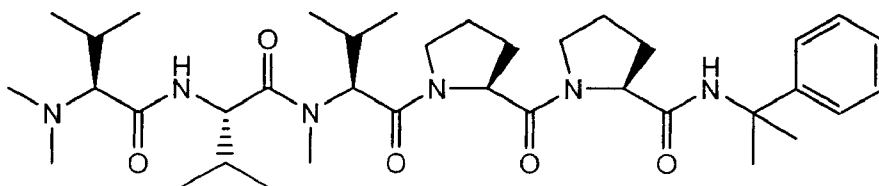




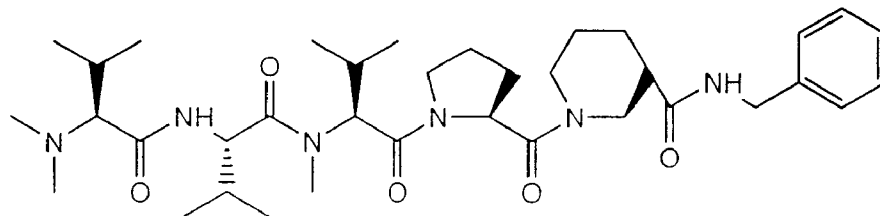
(ix)



(x)



(xi)



(xii)

